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INTRAOSSEOUS INFUSION INTO THE SKULL: DEVELOPMENT OF AN INTRA-CALVARIAL INFUSION SYSTEM (ICIS)

by

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DEDICATION

To Keith, for your inspiration

To Jodie, for your support

To Emma, for your motivation

ABSTRACT

Numerous sites have been utilized for the diversion and absorption of CSF, yet despite years of innovation, CSF shunt systems continue to have high complication rates. The calvarial diploë represents an alternative site for CSF diversion which has not previously been explored.

Various tracers were used to study the central delivery of fluids injected into the calvarial diploë of 14 crossbred adult pigs. Systemic uptake was determined from serial samples obtained from an indwelling central venous catheter.

Intraosseous absorption of fluids into the central circulation was demonstrated in all animals with delivery times similar to that following direct intravenous injection.

By demonstrating the ability of the calvarial diploë to absorb fluids into the central circulation, intraosseous infusion through the skull may represent a potential pathway to divert and absorb CSF. This may lead to the development of a shunt system that better restores a physiologic condition for CSF absorption.

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TABLE OF CONTENTS

Introduction		1
Chapter 1	Intraosseous Infusion	5
Chapter 2	Materials and Methods	26
Chapter 3	Histology	37
Chapter 4	Glucose Studies	45
Chapter 5	Technetium-99^{m} Studies	50
Chapter 6	FITC-Dextran Studies	53
Chapter 7	Infusion Pressure Studies	58
Chapter 8	Autopsy Studies	64
Chapter 9	Conclusions	70
Bibliography		72

LIST OF FIGURES

Figure 2-1	Screw-type Infusion Device	28
Figure 2-2	Manifold-style Infusion Device	29
Figure 2-3	Experimental Set-up	32
Figure 3-1	Scanning Electron Micrograph (SEM) of Porcine Skull	39
Figure 3-2	SEM of Inner Surface of Burr Hole	40
Figure 3-3	SEM of Threaded Burr Hole	40
Figure 3-4	SEM of High Speed Drill Burr Hole	41
Figure 3-5	SEM of Twist Drill Burr Hole	42
Figure 3-6	Higher Power SEM of Twist Drill Burr Hole	43
Figure 3-7	SEM of Curetted Burr Hole	44
Figure 4-1	Serum Glucose Following IO Infusion of 50 ml D50W	46
Figure 4-2	Serum Glucose Following IO Infusion of 20 ml D50W	47
Figure 4-3	Serum Glucose Following Injection of D50W	48
Figure 5-1	Gamma Activity of Blood Following Injection of Tc-99m	51
Figure 6-1	Serum Fluorescence Following IO Infusion of FITC-Dextrans	55
Figure 6-2	Serum Fluorescence Following Injection of FITC-Dextrans	56
Figure 7-1	Infusion Pressure Related to Controlled Rate of Infusion	59
Figure 7-2	Infusion Pressure Required to Deliver Fluids at Controlled Rates of Infusion	60
Figure 7-3	Infusion Pressure Related to Burr Hole Technique	61
Figure 7-4	Infusion Pressure for Intraosseous Infusion into the Porcine Skull versus the Human Skull at Autopsy	62
Figure 8-1	Photograph of Inner Surface of Calvarium	65
Figure 8-2	Photograph Showing Temporal Bone Thickness	65
Figure 8-3	Photograph of Intraosseous Infusion	67
Figure 8-4	Close-up Photograph Demonstrating Drainage from the Sagittal Sinus	67
Figure 8-5	Infusion Pressure Necessary to Infuse Fluids at Varying Rates	68

INTRODUCTION

Hydrocephalus, the accumulation of cerebrospinal fluid (CSF) within the skull, has been recognized since ancient times. Obstruction to the normal circulation or absorption of CSF leads to the retention of fluid upstream from the obstruction in much the same way as a dam prevents the flow of water along a river. Young children typically present with a rapidly enlarging head, developmental delay, and downward deviation of the eyes. Older children and adults may present with headaches, nausea, vomiting, and decreased level of consciousness. Left untreated, this condition leads to cognitive impairment, blindness and eventually death.

Hippocrates attempted to treat these patients by drilling a hole in the skull to drain the excessive fluid. Others tried wrapping the head in tight bandages to prevent the enlargement of the skull. Unfortunately for those with progressive hydrocephalus, there were few effective treatments. Considering the frequency of hydrocephalus today, there are relatively few reports prior to the 20th century.

During the late 1800s, much of our current understanding of the formation, circulation, and absorption of CSF as well as the anatomy of the ventricular system was revealed. In 1875, Ernst Axel Hendrik Key (1832-1901) and Magnus Gustav Retzius (1842-1919) proved that CSF is secreted by the choroid plexus, flows through the ventricular system before escaping into the subarachnoid space, and is ultimately absorbed through the arachnoid villi and Pachionian granulations into the dural venous sinuses. Tumors which block CSF circulation through the ventricular system lead to non-communicating or obstructive hydrocephalus. Failure of the arachnoid villi to absorb CSF leads to communicating hydrocephalus.

The true natural history of hydrocephalus is not well understood. While there is no denying that this disorder can be rapidly progressive and ultimately fatal, these cases are uncommon if not rare. During the first half of the 20th century, Walter Dandy (1886-1946) expanded the treatment options for patients with hydrocephalus. He was

the first to surgically remove the choroid plexus as a means of treating hydrocephalus. He also recognized the difference between obstructive and communicating hydrocephalus (which he referred to as internal versus external hydrocephalus) and treated obstructive hydrocephalus by open third ventriculostomy. Prior to the 1950s, few cases came to medical attention, and those that did likely represented the most severe along a spectrum ranging from benign enlargement of the subarachnoid space to rapidly progressive macrocephaly. Understandably, the outcome following medical or surgical intervention was poor as less severe cases went unrecognized.

With the development of silicone tubing and slit valves, internal diversion of CSF to some distal site for absorption – most commonly the peritoneal cavity – has improved the treatment of hydrocephalus. Unfortunately, relying on extracranial absorptive sites has inherent complications. Long catheters are required to shunt fluid from the ventricular system to the peritoneal cavity. The flow of fluid through a cylindrical tube is proportional to the radius of the tube and the pressure drop between the two ends, and inversely proportional to the length of the tube as revealed by Poiseuille's law.

$$\text{Flow Velocity} = \delta V/\delta t = \pi r^4 \Delta p/8\eta l$$

Thus, in designing a catheter for the diversion of CSF, both the radius and length of the tube will affect flow. Additionally, as an individual changes from a recumbent to an upright position, the change in pressure (Δp) between the two ends of the tube will affect flow. The net result is that a single tube, diverting CSF from the ventricles to the abdominal cavity, will fail to drain enough fluid while in the recumbent position and will over-drain in the upright position due to siphoning.

Numerous pressure control, flow control, and anti-siphon valves have been developed to address the concern of variable flow through a shunt with changes in body position. However, even the best shunt systems continue to have failure rates of up to 50% within two years, requiring frequent shunt revisions.

Additionally, internal diversion of CSF for distal absorption fails to address the important functions of CSF. Normally CSF serves as a hydraulic cushion for the brain, protecting it from the irregular surface of the cranial floor. CSF also functions to dissipate the arterial pulse with each heart beat as 1,000 ml of blood flows through the cerebral vasculature every minute. This arterial pulse pressure is not transmitted to the brain as the CSF pulses out of the skull through the foramen magnum with each beat. The dynamic circulation of CSF also maintains the extracellular environment for optimal neuronal function.

With the development of computed tomography (CT) and magnetic resonance imaging (MRI), as well as an increased awareness of hydrocephalus, early diagnosis is becoming more common. Given the variability of etiology, clinical presentation, and severity, it is important to consider alternative techniques for treating this disorder while recognizing the value in maintaining normal CSF volume and function. Over the past ten years, endoscopic third ventriculostomy has grown in popularity for the treatment of non-communicating hydrocephalus. By establishing an alternative pathway for CSF circulation and bypassing the obstruction, the functional volume of CSF is maintained and the natural absorption into the venous system via the arachnoid granulations is preserved. In cases of communicating hydrocephalus, the circulatory pathways are present; however, there is impaired absorption at the arachnoid granulations. Thus, a shunt system is necessary to allow the absorption of CSF. If the goal is to create a system that preserves the physiologic volume and function of CSF, alternatives to the current extra-cranial diversion for absorption must be sought in order to avoid overdrainage. The body naturally adjusts the differential pressure for CSF absorption across the arachnoid granulations into the venous system. In the recumbent position, the venous system of the head and neck is distended allowing passive blood return to the heart. In the upright position, venous return initially increases which decreases the pressure in the dural sinuses (thus increasing the pressure differential for CSF absorption); however, the neck veins then collapse which maintains the venous pressure within the dural sinuses. The inherent wisdom

of the venous system of the head and neck to maintain venous pressure is essential to normal CSF hydrodynamics. Is it possible to create a shunt system that bypasses the arachnoid granulations while maintaining the differential pressure for CSF absorption established by the venous system?

As early as 1907 Erwin Payr (1871-1947) attempted drainage from the ventricles directly into the dural venous sinuses, thus bypassing the arachnoid granulations in patients with hydrocephalus. Unfortunately, as with most patients treated at that time, the outcomes were poor. More recently, a number of centers have attempted CSF diversion directly into the superior sagittal sinus using a percutaneous technique which has shown promising early results.[1-3] However, placing a catheter into the sagittal sinus has significant risks including massive hemorrhage or delayed thrombus formation. An alternative indirect access to the dural sinuses may be possible through richly vascular skull. Fox et al.[4] demonstrated the anatomic communication of the parasagittal lacunae laterales with the superior sagittal sinus. Corrosion casting by Johnston et al.[5] demonstrated the connection between skull diploic space and the superior sagittal sinus. The following research was designed and conducted to investigate the physiologic vascular communication of the skull with the dural sinuses and the venous system of the head and neck, as well as to develop an intraosseous infusion device that would be suitable for the calvarial diversion of CSF for the management of hydrocephalus.

CHAPTER ONE
INTRAOSSEOUS INFUSION

Intraosseous infusion was widely used during the 1940s and early 1950s, particularly in pediatric patients owing to the difficulty of obtaining and maintaining intravenous access, for delivery of blood, crystalloid fluids, and medications. However, there were concerns regarding the potential for cellular damage and growth disruption of long bones used for intraosseous cannulation, as well as complications such as osteomyelitis at the site of infusion and fat emboli from the marrow cavity. The development of plastic catheters in the 1950s greatly simplified vascular access in all patients, and the use of intraosseous needles fell largely out of favor for the next three decades. A number of reviews written in the 1980s commenting on the difficulty of inserting intravenous cannulae in children, particularly in cases of circulatory collapse, led to renewed interest in intraosseous infusions. The use of intraosseous needles for obtaining vascular access is now the standard of care in pediatric critical care hospitals if there is any delay in obtaining venous access. This review explores the history of intraosseous infusion, its development through animal models and clinical practice, and the concerns regarding potential complications. Finally, a potential new application for intraosseous infusion through the skull is discussed.

Historical Perspective

At the turn of the last century, the hematologic function of the bone marrow was understood; however, the mechanism by which mature blood cells entered the circulation from the marrow cavity was not fully appreciated. In 1916, Drinker and Drinker isolated the tibia with its arterial supply preserved to evaluate the vasomotor control of the marrow. Fluids were continuously infused through the nutrient artery while the outflow was collected and measured. They demonstrated that the administration of epinephrine through the nutrient artery or stimulation of the accompanying nerve resulted in diminished efflux of fluid from the tibia due to vasoconstriction of the marrow vessels.[6] They followed in 1922 with a description of

the delivery of blood cells from the bone marrow to the blood stream.[7] In their detailed description of the circulation through the bone marrow in mammals, they described the structure of the marrow cavity as composed of five main elements: a delicate marrow framework, fat cells, developing and adult blood cells, blood vessels, and interstitial fluid. The stromal framework, fat and blood cells, they argue, are incompressible and relatively immobile; in contrast, in response to changes in intraosseous pressure, the circulating blood and the interstitial fluid are mobile through the marrow space and marrow vessels as well as across endothelial membranes. This discovery led to the idea that fluid injected or infused into the marrow cavity would cause the pressure within that space to increase with the resultant movement of interstitial and infused fluid across the endothelial membrane into the general circulation.

Through the 1930s and 1940s, numerous studies demonstrated that fluids and drugs injected into the marrow cavity were rapidly absorbed. Josefson attempted to treat 12 patients with pernicious anemia by injecting liver concentrate directly into the sternum. Contemporary treatment by intravenous delivery of liver concentrate caused transient headaches accompanied by vomiting as a common side effect, prompting Josefson to attempt direct stimulation of the bone marrow through intraosseous injection. He noted that these patients experienced symptoms similar to those who received intravenous injections, probably owing to the rapid absorption of the drug from the marrow.[8]

In 1936, while conducting experiments on bone marrow transplantation in rabbits, Tocantins made an interesting observation. He injected 5 ml of salt solution into the proximal end of the femur and observed only 2 ml recovered at the distal end. As no evidence of extravasation of fluid into the muscle and other tissues adjoining the area of injection could be identified, he believed that at least some fluid injected into the marrow cavity of long bones was readily absorbed.[9] Based on these observations, Tocantins went on to study the fate of substances injected into the bone marrow and found that substances injected into the marrow cavity of the tibia in rabbits and the

sternum in man are almost immediately absorbed into the general circulation.[10] His first experiments were to determine if blood volume could be replaced by the intraosseous route. Nine rabbits were bled of 20% of their circulating blood volume by cardiac puncture and slow aspiration. Twenty-four hours later, the same volume of blood was returned through the proximal tibia at a rate of 5-7 ml per minute in seven experimental animals. Six of the seven animals showed recovery of hemoglobin and erythrocyte count to baseline within 48 hours. One rabbit died as a result of a hemopericardium. He then demonstrated that rabbits made hypoglycemic by injection of insulin could be treated by intraosseous infusion of dextrose. Severe induced hypoglycemia led to seizures in five experimental animals. Four animals were treated with 25% or 30% dextrose injected into the marrow of the proximal tibia at an average rate of 8 ml per minute. The treated animals all recovered from the hypoglycemic seizures while one untreated control animal died 37 minutes after the first convulsion. Finally, he attempted to study the absorptive capacity of the sternum in three adult male subjects. In two, a salt solution ran in readily at infusion rates varying between 5-10 ml per minute. This was maintained for up to 30 minutes by gravity infusion; however, the height of the fluid reservoir, and therefore the infusion pressure, was not mentioned. The third subject experienced "bone pains", and no fluid could be infused. The success of these experiments led Tocantins to conclude that "the medulla of bones may, therefore, offer one more route for parenteral therapy when quick absorption is desired."[10]

These early experiments led to the widespread use of intraosseous infusion, particularly for fluid resuscitation in children. At that time, needles used for intravenous access were easily dislodged or advanced interstitially requiring repeated venipuncture, while intraosseous needles were relatively easy to use and had a low complication rate. The use of intraosseous infusion continued, however, to raise concerns over potential complications such as infection, extravasation of fluid, fat emboli, and potential damage to the epiphyseal growth plate of long bones and its use fell out of favor in the 1950s. The advent of plastic intravenous catheters and refined technique for inserting peripheral venous lines simplified intravenous access and

facilitated prolonged continuous infusion or intermittent injection with a single venipuncture.[11] Unfortunately, peripheral intravenous catheters continue to have numerous limitations and risks. Extravasation of fluids, limited rate of infusion, and delay or failure in obtaining vascular access are the early concerns associated with placement of intravenous catheters.

Pediatric patients present the greatest challenge for securing vascular access. They are less cooperative, their vessels are smaller and covered by more subcutaneous tissue, and in cases of shock and vascular collapse their veins are even more difficult to find. In one pediatric medical center, placement of an intravenous catheter required 10 minutes or more in 24% of children in cardiac arrest, and in 6% intravenous access was never achieved.[12] These limitations of peripheral vascular access can have significant clinical impact. In cases of shock, severe burns, cardiac arrest, and sepsis where there is often significant circulatory collapse, obtaining rapid and reliable vascular access is essential. Venous cut-downs are time consuming. Insertion of central venous catheters adds the additional risk of vascular injury, pneumothorax, and thrombus formation, with potentially fatal consequences. Due to these issues, a number of articles reviewing vascular access and the role of intraosseous infusion have been published in the past twenty years again advocating the use of intraosseous infusion in children.[9, 13-20] The focus of these reviews has been on the ability of intraosseous lines to provide vascular access quickly and reliably for use in pediatric resuscitations. Improved treatment of cardiac arrest, as well as shock secondary to hypovolemia or sepsis requires rapid and reliable vascular access. The current guidelines for the resuscitation of infants and neonates recommend intraosseous access for medication and volume expansion if there is any delay in obtaining direct venous access.[21, 22]

The renewed interest in intraosseous infusions has led to the development of numerous new intraosseous infusion devices. Wagner and McCabe studied the success of establishing intraosseous infusion by inexperienced residents using different intraosseous needles.[23] They found an overall success rate of 68% within two minutes and no significant difference between standard hypodermic, spinal, bone

marrow, and Turkel intraosseous infusion needles. This success rate is much lower than the 98% reported by Heinild[24] or Tocantins[25] indicating that training and experience obtaining intraosseous access may be an important factor. Certainly, Heinild reported that 60% fewer unsuccessful attempts were registered in hospitals that used the technique more frequently.

As new infusion devices became available, studies demonstrated that practice and prior experience obtaining intraosseous access improved success rates. The bone injection gun (BIG – TEIC Ltd. Science Park Technion, Nesher, Isreal), an automated device for insertion of a 15-gauge sterile trocar by a precharged coil, was developed to simplify intraosseous access. Using this device, specifically trained personnel established intraosseous infusion into the tibial tuberosity (76% of cases), the lateral and medial malleolus, and the distal radius with 100% success.[26] No local or systemic complications were observed from radiographic and clinical follow-up of up to 4 months. Jun et al. then compared a screw-tipped intraosseous needle (Sur-Fast – Cook Critical Care, Bloomington, IN) versus a standard bone marrow needle and demonstrated an improved success rate (95% vs. 79%) using the Sur-Fast needle once medical students had gained experience with intraosseous access.[27] However, without practice or experience, students were slower and found the Sur-Fast needle to be more difficult. A new system for sternal intraosseous infusion in adults, the First Access for Shock and Trauma (FAST 1 – Pyng Medical Corp., Vancouver, BC, Canada) intraosseous infusion system was evaluated by Macnab et al.[28] They reported a success rate of 84% overall in a pilot study of the first 50 uses of the system for emergency intraosseous access in adults. With experience, the success rate improved from 74% to 95%. They also demonstrated that infusion rates of 80 ml/min (gravity infusion) to 150 ml/min (syringe infusion) were tolerated with no complications at 2 months follow-up. Calkins et al. directly compared the success rate and time to intraosseous placement for the BIG, Sur-Fast, FAST1, and Jamshidi needles for use in the military Special Operations environment.[29] Following specialized instruction on the use of each system, all four devices were shown to be easy to learn as well as easy to place. The FAST 1 system was successful in 97% of cases with a mean time to placement of 114 seconds. The BIG was successful in 94% of cases with a mean

placement time of 70 seconds. The success rate for the SurFast and Jamshidi needles was 97%, taking an average of 88 seconds, and 90 seconds respectively. These studies demonstrate the overall ease of use and high success rate of intraosseous infusion devices as well as the importance of appropriate training and experience in the use of these systems.

Anatomy and Physiology

The marrow cavity remained inaccessible and devoid of direct physiologic study until 1916 when Cecil and Katherine Drinker perfused the tibia and demonstrated humoral and neural vasomotor control over the circulation to the marrow cavity in dogs. Using a constant pressure and continuous flow perfusion apparatus, they demonstrated that the venous outflow from the tibia was drastically reduced following the administration of epinephrine through the nutrient artery. Electrical stimulation of the nerve to the marrow caused vasoconstriction and led to a similar reduction in venous outflow.[6] Drinker et al. later conducted a more comprehensive series of experiments measuring the blood flow and perfusion of the canine tibia under greatly increased pressure and rate of blood flow.[7] These studies were the first to describe the circulation through the bone marrow by infusing fluids through the nutrient artery.

The ability of bones to absorb infused fluids into the systemic circulation is based on their rich vascularity and communication with the venous system. The marrow cavity consists of a stromal meshwork containing fat cells, developing blood cells, interstitial fluid and blood vessels.[7] Fluids or drugs injected into the medullary space rarely diffuse more than a few centimeters before entering the venous circulation via medullary venous channels draining into nutrient and emissary veins.[15, 30, 31] The final venous drainage sites from the tibia and sternum are the deep femoral and internal mammary veins, respectively.[10] In clinical studies, Heinild et al. and Tocantins and O'Neill found that the resistance to infusion often subsides after infusion of the first 20 to 30 ml of fluid.[24, 32] Fluids may then infuse by gravity or by pressure with the resistance to infusion related to the diameter of the infusion needle, the viscosity of

the fluid infused, and the absorptive capacity of the bone. Tocantins and O'Neill went on to develop a method of determining intraosseous pressure, noting that the intramedullary pressure corresponded closely with the venous pressure of the draining vein.[32]

To investigate the rapid absorption of fluid from the marrow cavity, Tocantins injected Congo Red dye through an intraosseous needle in the proximal tibia. Serial blood samples taken by cardiac aspiration were positive for the dye within 10 seconds. He then injected mercury into the tibia of the rabbit to demonstrate the anatomic pathway of fluid absorption. Radiographs demonstrate the presence of mercury in the marrow cavity and draining via emissary veins into the deep femoral vein. The absorptive pathway from the sternum was then demonstrated in a female patient by injecting mercury under slight pressure into the manubrium and demonstrating mercury draining from the internal mammary veins.[10]

It is interesting to note that while early clinical studies made use of the medullary space of the manubrium in adults and older children due to its relatively larger marrow cavity and more rapid flow rate, pediatric and neonatal intraosseous infusion, utilizing the tibia became the most predominant focus of this technology.[32] In children under the age of three years the marrow cavity of the sternum is under developed for accepting intraosseous infusion.[24, 32, 33] Also, the major vascular structures deep to the sternum may be injured if the needle is advanced completely through the sternum. The larger marrow cavity of the proximal tibia or distal femur provides the optimal site for infusion, given that landmarks are readily palpable, major neural and vascular structures can be avoided, and the limb can be immobilized during the procedure.

The highly vascular red marrow of long bones, thought to be essential for intraosseous absorption, undergoes physiologic replacement by less vascular yellow marrow after about five years of age.[34] The sternum, however, retains its red marrow into adulthood. Thus, while the proximal tibia or distal femur may be preferred sites

for pediatric intraosseous infusions, the sternum is more reliable in adults. Other sites which have been used for intraosseous infusion include the humerus, clavicle, and iliac crest, all sites with a functioning hematopoietic marrow cavity.[35] A recent case report of intracalcaneal infusion challenged the assumption that a functioning medullary cavity is required for successful intraosseous infusion.[36, 37] McCarthy et al. went on to demonstrate that intraosseous infusion does not require a medullary cavity by injecting methyl green dye into the calcaneus and radial styloid in cadaveric specimens and observing the dye in the peripheral veins proximal to infusion.[38] They hypothesized that fluid infused into cancellous bone causes an increase in intraosseous pressure, and a movement of interstitial fluid out of the bone via the emissary veins. This is in keeping with the early work by Drinker et al. that the interstitial fluid and blood are mobile components of the intraosseous environment, while the fat cells and developing red and white blood cells are relatively immobile.[7]

Numerous animal studies have demonstrated the physiologic response to fluids administered via intraosseous injection. Tocantins early experiments demonstrated the restoration of hemoglobin and erythrocyte count following intramedullary injection of fresh blood into the sternum of rabbits.[10] Intraosseous resuscitation was confirmed in a dog that was bled of 20% of its circulating volume with a corresponding decrease in blood pressure. Citrated blood was syringe injected into the sternum, resulting in a return of blood pressure to baseline levels.[33] The usefulness of fluid resuscitation via intraosseous infusion was demonstrated in a piglet model of hypovolemic shock.[39] Twelve animals were bled to a mean arterial pressure of 30 mm Hg then randomized to one of three experimental groups. Resuscitation followed by central or peripheral intravenous infusion, or intraosseous infusion, with a saline solution injected manually at 50 ml/min for 20 minutes. They found no significant difference in mean arterial pressure, central venous pressure, or cardiac output following resuscitation between experimental groups. The pressure required for intraosseous infusion of saline at 50 ml/min was 450-475 mm Hg. Histologic examination of two of the tibias used for infusion revealed cellular washout and necrosis adjacent to the infusion site. These authors did not investigate the maximal

rate of intraosseous infusion nor the histologic changes related to rate or pressure of infusion. Cameron et al. went on to compare the central circulation delivery times of Technetium 99^{m} following peripheral intravenous and intraosseous injection into the tibia.[40] In euvolemic dogs, the mean transit time to the central circulation was less then 10 seconds in both experimental groups. In hypovolemic animals, the delivery time to the central circulation was slightly slower (12.79 seconds vs. 9.07 seconds) following intraosseous injection.

To investigate the mechanisms regulating bone perfusion, Kiaer et al. measured the arterial pressure, intraosseous pressure, and intraosseous PO_2 and PCO_2 of eight adult rabbits made progressively hypotensive by blood aspiration.[41] They found that intraosseous pressure followed the drop in arterial pressure in a linear fashion; with intraosseous pressures 3.5 times lower than arterial pressures. Peripheral and central venous pressures were not measured. They concluded that intraosseous blood flow is determined by arterial pressure and in cases of shock, hypotension leads to a decrease in intraosseous perfusion. However, an advantage of the marrow vessels is that they function as non-collapsible veins in the presence of hypovolemia and profound circulatory shock.[13]

Rate of intraosseous infusion is an important consideration if this technique is to be useful for fluid resuscitation. Shoor et al. measured the rate of infusion of normal saline into the bovine tibia under varying infusion pressure.[42] They measured intraosseous infusion at 10 ml/min under gravity infusion at 81 cm H20 (60 mm Hg). By increasing the infusion pressure to 300 mm Hg, they were able to increase the rate of infusion to 41 ml/min. Schoffstall et al. determined that flow rates were related to the size of the animal, the size of the infusion needle, and the pressure of infusion.[43] However, Hodge et al. argued that while infusion pressure and needle size significantly affect infusion rate, the differences are not clinically significant.[44] They assert that the rates are dependent on flow through the bone marrow rather than the size of the needle. Other factors, such as venous pressure and venous valves in the

draining veins in addition to flow through the bone marrow may influence intraosseous flow rates.[45]

In addition to blood and fluid resuscitation, intraosseous infusions have been used for the administration of anesthetics, analgesics, anticonvulsants, antibiotics, and vasoactive drugs.[46] While the majority of these studies have reported on the successful use of the intraosseous route for short term drug administration, Chastagner et al. evaluated an intraosseous infusion device for long-term use.[47] The implantable device was useful for antibiotic administration for six months with reliable and consistent flow rates throughout the duration of the study.

Clinical Studies

Following the discovery of the circulation through the medullary space of long bones and Tocantins' early research into the absorption of substances injected into the sternum, the use of intraosseous infusion for clinical application was considered. At that time, only the peritoneal cavity or the superior sagittal sinus, reached through the anterior fontanel, were available as alternatives to intravenous fluid administration. A clinical trial followed, in which 14 patients demonstrated 16 successful infusions using citrated blood, plasma, glucose, and saline at infusion rates of 0.4-9 ml per minute. Up to 1050 ml of fluid were given with no adverse reactions and only one attempted infusion failed.[48] Subsequent studies continued to demonstrate success in adult and pediatric patients.[25, 32, 33] Fifty-six infusions were attempted on 38 adult patients, of which fifty-three were carried to completion. One patient, in whom it was not possible to inject fluid into the sternum at three separate levels, was found at autopsy to have a marrow cavity that "was small, dense, and with little marrow in it, the bone itself being unusually hard."[32] The average rate of flow by gravity into the manubrium of the sternum was 3.4 ml/min with a range from 0.4 to 25 ml/min. Infusion into the body of the sternum ranged from 0.4 to 9.1 ml per minute with an average rate of 3.1 ml/min.[33] In these patients, up to 6,800 ml of various fluids was infused over a period up to thirty hours with no report of any immediate or delayed

local or constitutional reactions. The authors go on to report that while the sternum (manubrium or body) is the preferred site of infusion in adults, in infants and children under the age of three, the marrow space of the sternum is underdeveloped and unsuitable for such infusion. They recommend the medial surface of the proximal tibia, due to the absence of significant blood vessels, nerves, and subcutaneous fat. Alternative sites for infusion include the distal femur and distal humerus. When the clavicle was used the flow was disappointingly slow.[32] Intraosseous infusions into the proximal tibia or distal femur was attempted on eleven children under the age of 2 years. Fourteen attempts were successful in 9 of the 11 children, with 13 failed attempts. Seven of the 13 failed attempts were on two children where no intraosseous infusion proved possible. The fluid reservoir was stationed 1 to 1.5 meters above the point of entrance of the needle and by this technique the flow rate of infusion ranged from 0.5 to 8.0 ml/min. The total duration of infusion ranged from 7 to 255 minutes, with 30 to 400 ml of citrated blood or saline infused.[33] The two patients where intraosseous infusion failed had congenital hemolytic anemia and erythroblastosis with unusually dense bones and a narrowed marrow cavity. As with the adult infusions, there were no adverse reactions in any of the pediatric patients receiving intraosseous infusion. A larger study examining 79 infusions in 52 children from 2 days to 5 years of age yielded only a single adverse reaction. A contaminated dressing over the puncture site in the distal femur led to a superficial pustule that required simple incision and drainage. In this paper, the authors suggest that intraosseous infusion of fluids should not exceed 4 ml/min to prevent "overloading of the marrow, with possible injury. Like the peripheral veins, the emissary marrow veins are small and delicate and do not (tolerate) excessive rates of flow."[25]

Heinild et al. published the largest clinical series of pediatric intraosseous infusions from seven pediatric clinics in Denmark.[24] In the period from 1943 until 1946, a total of 982 intraosseous infusions were conducted on 495 patients aged 2 days to four years, with only 18 failures (1.8%). The maximal rate of infusion was 10 ml per minute usually by syringe bolus infusion, though continuous infusion for up to 32 hours was given to 5 patients. Seventy-two of the 495 patients were selected at

random for roentgenographic follow-up. Thirty-six patients were examined within one year of the infusion, 18 patients between one and two years, and 18 were examined more than two years from the infusion. Of the 36 patients examined within one year of intraosseous infusion, six showed noticeable sites of puncture with marginal sclerosis. This finding was never observed more than six months after the infusion, and in the 36 patients examined more than one year following infusion there were no roentgenologic abnormalities, and "in every instance the growth of the bone had proceeded normally on both sides." Of importance from this study is the low rate of infection in the absence of sterile technique. Overall, there were only five cases of osteomyelitis (1%); however, three cases occurred in a subset of 23 patients receiving 32 infusions of 50 per cent glucose (13%). They reviewed the literature and found 7 cases of osteomyelitis out of 220 infusions, all associated with continuous infusions. Thus, the risk factors for developing local infections related to the site of infusion included continuous infusion and injection of hypertonic glucose. The severity of patient illness, the injection of non-sterile fluids, and the lack of aseptic technique are all significant confounding factors to this conclusion. By comparison, bacterial colonization of central venous catheters in place for 1 to 14 days is as high as 81%, leading to catheter related sepsis of 1.4% to 3.5% in critically ill children.[16]

Recent clinical reports have described the success of intraosseous infusion using the clavicle and sternum.[35, 49] Intraosseous infusion has even been shown to be successful in preterm neonates as small as 800 grams.[50, 51]

Technique

The advantages of intraosseous infusion over percutaneous cannulation or venous cut-down are the easily identifiable landmarks and relative simplicity of intraosseous access. Initially described in the 1940s for intraosseous access into the sternum (body and manubrium) or the proximal tibia, the same technique can be modified slightly for placement in other sites.[10] Care must be taken to reduce the risk of infection and prevent air emboli into the systemic circulation. These concerns have greater

importance for intraosseous infusions as compared with peripheral venous lines as the management of osteomyelitis often requires local debridement and prolonged antibiotics, while local thrombophlebitis and cellulitis can be treated by removing the offending IV cannula followed by a short course of antibiotics. Air entrainment through an intraosseous needle can lead to clotting of marrow within the needle or creating an "air-lock" occlusion, thereby limiting or preventing adequate infusion of fluid. To limit these risks, IV tubing should be flushed with sterile crystalloid fluid prior to placement of the intraosseous needle and the skin over the puncture site should be cleansed with alcohol or an antibacterial scrub and, if necessary, shaved.

The landmarks for insertion vary depending on the site of infusion. The proximal tibia, medial to the tibial tuberosity, is the most commonly used site for intraosseous infusion. This site has a broad flat surface and bone is easily palpated owing to the thin covering of skin. In children up to the age of 5 or 6 years, the cortex of bone is relatively thin and easily penetrated. After this age, the distal tibia may be a more useful site for intraosseous infusion as the cortex and overlying skin remain thin.[13, 31] The intraosseous needle is pushed perpendicular to the bone until the skin and subcutaneous tissues have been punctured and the needle is positioned against the periosteum. The needle is then advanced through the outer cortex of bone by a gentle back and forth screwing motion with care taken to ensure the force is directed along the long axis of the needle to cleanly puncture the bone. When inserting the intraosseous needle into long bones, the angle if insertion is 30° to 60° toward the metaphysis to avoid potential injury to the growth plate. Insertion into the sternum is perpendicular to the flat surface of the body or manubrium. A "pop" is felt upon penetration of the outer cortex of bone, and the needle should be able to stand unsupported.[20, 24] The stylet is then removed from the needle and a saline filled syringe is attached for aspiration of marrow to confirm placement. If marrow blood cannot be aspirated, the needle is not within the marrow cavity – either too deep and through the bone, or too superficial and still within the cortical bone. Suboptimal needle placement may lead to extravasation of fluid, local cellulitis, compartment syndrome, and importantly, failure to deliver fluid and medication for resuscitation.

Also, when the marrow is insufficiently vascular, aspiration of blood may be difficult or limited. Tocantins and O'Neill felt that if no marrow could be aspirated, it was unlikely the site would be valuable for infusion.[32] Alternatively, the inability to aspirate blood or bone marrow from the intraosseous needle may reflect severe hypoperfusion, dehydration or hypovolemia.[20] Additional attempts at intraosseous puncture in the same bone are contraindicated as this may result in extravasation of fluid from the other puncture site. Once marrow has been aspirated, the IV tubing is quickly attached, with care taken to exclude air from the system before infusion begins. The bone marrow is highly coaguable and it is important that the infusate flow continuously to prevent back-up of marrow and clotting within the needle.[24, 25, 32] Flushing with a heparinized saline solution prior to intraosseous infusion may help prevent clotting of marrow blood.[52]

Placement of an intraosseous needle into the body or manubrium of the sternum has the additional risks of injury to the underlying vascular structures in the chest.[13] The FAST 1 was developed to simplify placement in the sternum. A target patch is placed on the manubrium and a hand-held introducer is used to insert a flexible infusion tube with a stainless-steel tip to a predetermined depth.[28, 49] An automated infusion device is practical since the sternum has a reliable cortical thickness and a uniform marrow space.[28] Automated intraosseous infusion devices have also been developed for use in the tibia, femur, or other long bones to simplify insertion and reduce insertion times.[26, 27, 29]

Indications and Complications

Early reports of intraosseous infusions commented on the indications, contraindications, and potential complications associated with intraosseous infusion. The guidelines for the use of intraosseous vascular access recognize that "an intaosseous cannula provides access to a noncollapsible marrow venous plexus, which serves as a rapid, safe, and reliable route for administration of drugs, crystalloids, colloids, and blood during resuscitation."[17] Intraosseous infusions are in

widespread clinical use for pediatric and neonatal resuscitations when there is any delay in obtaining intravenous access.

There are few absolute contraindications to intraosseous infusion. These include osteogenesis imperfecta, osteopetrosis, and an ipsilateral fractured extremity, because of the risk of subcutaneous extravasation of infused fluids. Infants with congenital hemolytic anemia and erythroblastosis have unusually dense bone with a narrowed marrow cavity, which may limit the success of intraosseous infusion in these patients.[33] Other relative contraindications include burns or cellulitis over the site of infusion and systemic septicemia. In contrast, recent reviews recommend intraosseous infusion in pediatric cases of burns and sepsis due to the relative ease of access in these patients compared with intravenous cannulation.[13, 15, 17, 31]

Many complications have been described using intraosseous infusions. Failure to enter the bone marrow cavity or incorrect placement leading to extravasation of fluid has been reported in 0% to 18% of cases.[11] This may be due to misplacement of the needle within the skin and subcutaneous tissues with incomplete penetration of the cortex, or over-penetration through the opposite cortex, into the underlying soft tissue. Excessive rocking of the needle during insertion causing a larger hole or repeated attempts at intraosseous access in the same bone can also lead to extravasation of infused fluids. Several case reports have described this potentially devastating complication leading to compartment syndrome and necrosis requiring fasciotomy and even amputation.[53-56] Automated infusion devices, screw designs, and improved needles currently under development may simplify intraosseous access and reduce the risk of fluid extravasation in the future.[27, 57] Meanwhile, meticulous care to insert the needle appropriately on the first attempt, stabilizing the limb and IV tubing to minimize accidental dislodgement and careful monitoring for signs of extravasation are essential to prevent this potentially major complication. In a canine study, Günal et al. secured spinal needles into the tibia using bone cement to prevent extravasation of fluids from the puncture site, then infused radiopaque dye at the rate of 480 ml per hour while monitoring pressure in the anterolateral compartment of the leg. After approximately 360 ml had been infused, the compartment pressures rose

from 5 to 7 mm Hg at rest to over 35 mm Hg and then continued to rise as more dye was infused. Roentgenographs taken at this time demonstrated dye in the soft tissues.[58] The authors argue that as fluid is infused into the marrow cavity, the intraosseous pressure increases, leading to leakage of fluid from periosteal capillaries into the surrounding tissue by hydrostatic pressure. This study suggests that a dose and time dependent relationship exists in the development of compartment syndrome with intraosseous infusion; however, compartment syndrome in clinical practice has proven to be a rare complication. This study described fluid infusion at the rate of 8 ml/min, which may have exceeded the absorptive capacity of the canine tibia. Tocantins et al. had also cautioned against flow rates greater than 4 ml per minute – especially in children, to prevent overloading the marrow and causing injury to capillaries and draining emissary veins.[25]

The theoretical concerns of air embolism and damage to the physis have not been demonstrated in clinical studies. Careful technique of preparing IV tubing and fluids and appropriate placement of the intraosseous needle should prevent introduction of air into the system. Numerous studies have investigated the risk of histologic and physiologic damage to long bones used for intraosseous infusion. Tocantins et al. examined 19 pediatric patients up to twenty-one months following intraosseous infusion without any roentgenographic abnormalities.[25] Heinild et al. investigated 36 patients less than one year after intraosseous infusion and noted marginal sclerosis at the puncture site in six patients, but never later than six months after the infusion. A further 36 patients were examined later than one year from intraosseous infusion, with no abnormalities found. Furthermore, 11 patients died within two weeks of the infusion, allowing careful examination of their tibial insertion sites. Except for a small hole at the puncture site, no abnormal features were identified and specifically, the epiphyseal line was found to be normal in all cases.[24]

Numerous animal studies of intraosseous infusion have been conducted to look at the immediate and long term effect on bone. Bielski et al. examined the effect on the immature physis in an experimental rabbit model by infusing normal saline, sodium

bicarbonate, or dopamine for a duration of 3 to 22 minutes.[59] Tibial infusion sites examined within 24 hours showed evidence of hematoma formation and disruption of the normal trabecular structure, confined to the metaphysis. These changes were not present at tibial infusion sites examined three weeks after infusion suggesting that morphologic changes in response to intraosseous infusion are temporary. There was no evidence of growth disturbance or any histologic changes in the epiphyseal growth plate. However, there was no report of the volume of fluids infused or the pressure of infusion, and this study gives no indication of potential histologic changes associated with prolonged infusions. Earlier studies examining the long term effects of intraosseous infusion in weanling pigs found no radiographic difference in epiphyseal growth plate closure between the experimental and control limbs and demonstrated no significant marrow injury.[60, 61] The effect of hypertonic fluid infusion, as well as rate of infusion was subsequently studied by Brickman et al.[62] Sixty pigs received intraosseous infusion of mannitol or saline into a front forelimb by slow (5 to 12 ml/min) or fast (20 to 50 ml/min) infusion for no longer than 20 minutes. The only complication observed at the time of infusion was mild extravasation of fluid in the animals receiving hypertonic fluid at a rapid infusion rate, believed to be due to the increased infusion pressure required in this group. Animals were observed for 4 to 5 months without any developmental problems, ambulatory difficulty, or signs of infection. Histologic examination identified gross lesions consisting of periosteal new bone formation, cortical distortion, and medullary sclerosis in the hypertonic groups. However, histologic lesions ranging from mild focal fibrosis to marrow degeneration and necrosis of fat were seen in the experimental limb of only two animals, one from the rapid hypertonic group and one from the rapid isotonic group. Thus, it appears as though rate of infusion, while potentially affecting extravasation rate, has no effect on the long-term gross or histologic appearance of long bones. The tonicity of fluid may cause gross lesions but these are not clinically significant. Sodium bicarbonate is a hypertonic sclerosing agent that has been used to study the effects of intraosseous hypertonic fluids on marrow contents. Spivey et al. injected 1 mEq/kg (1 mEq/ml) into the tibia of swine using an 18-gauge spinal needle and injected 1 ml/kg saline into the other tibia to serve as a control to observe the animals for signs of

osteomyelitis as well as for histologic examination.[63] Standard anterior-posterior and lateral roentgenographs and triple-phase technetium^{99m} bone scans were obtained 30 days after infusion. Radiologists blinded to the infusions were unable to determine which tibias received sodium bicarbonate or which received saline. Specifically, no focal osseous abnormalities were identified other than a mild radiodensity seen in the cortex of a single tibia that corresponded to the needle puncture site in an animal that received sodium bicarbonate. The histologic examination revealed normal bony matrix and cellular composition and the absence of an inflammatory response in all samples. A subsequent study suggested that intraosseous infusion of sodium bicarbonate led to intracortical necrotic foci, loss of bony interstitial lamellae, and interstitial foci of fibrous connective tissue consistent with local increase in skeletal turnover.[64] However, each of these studies examined only five animals that received only low volume infusions over very short duration. Continuous intraosseous infusions were evaluated in the caprine tibia by Welch et al.,[65] using surgically inserted Osteoport pediatric implants. Baseline intraosseous pressures were 11-21 mm Hg (mean 15.6 mm Hg). Ten animals were divided into three experimental groups: group 1 received continuous infusion of citrated blood 24 hours/day for 5 days at infusion rates adjusted to maintain an intraosseous pressure two to three times the baseline value. This corresponded to infusion rates of 12-20 ml/min (mean 17.5 ml/min); group 2 animals underwent high-pressure infusion of 5 ml lactated ringers solution within 5 seconds every 12 hours for a total of 10 days. The intraosseous pressure measured during the infusion period ranged from 90 to 125 mm Hg, and would remain elevated for up to 45 seconds before returning to baseline; group 3 animals served as positive controls. The patency of the Osteoport was maintained by injection of 1.5 ml heparinized saline (50 IU/ml) using minimal pressure every three days. Two additional animals served as sham surgical controls and did not have Osteoports implanted. Animals receiving continuous intraosseous infusion demonstrated only minimal clinical signs of limb discomfort evidenced by slight limb movement and head turning toward the infused limb, while animals in group 2 demonstrated limb withdrawal and attempts to resist limb restraint during infusion suggesting that high intraosseous pressure causes significant limb discomfort. By

using a subcutaneously placed intraosseous access device, sterile surgical technique, and preoperative antibiotics, they were able to prevent septic complications in all of the experimental animals. Many bone histologic and morphometric changes resulted from intraosseous infusions including periosteal, endocortical, and cancellous new bone formation, as well as marrow fibrosis, that were most evident in animals receiving continuous infusion. The authors concluded that sustained elevations in the intraosseous pressure led to greater bony remodeling than intermittent extreme elevations of intraosseous pressure and that the new bone formation and marrow fibrosis could eventually decrease intraosseous infusion flow rates. However, they did not determine if intraosseous infusion at rates maintaining near basal intraosseous pressure would lead to similar bony remodeling.

Early clinical studies on the efficacy and safety of intraosseous infusions warn of the possibility for fat and bone marrow emboli; however, there have been no reports of clinically significant pulmonary emboli. In children, the highly vascular red marrow is replaced by a more fatty yellow marrow after five years of age. This transition explains the rationale for utilizing long bones for intraosseous infusion in children and the sternum (which retains a greater hematopoetic function throughout life) in adults. It may also explain the lack of clinical evidence for pulmonary emboli.
Orlowski et al.[66] examined autopsy pulmonary specimens on two children who had received intraosseous infusions during resuscitation but died within four hours, finding up to 0.71 bone marrow and fat emboli/mm^2 of lung. They then examined the degree of bone marrow and fat emboli following intraosseous infusions of saline and various resuscitative fluids in thirty dogs. Using hematoxylin and eosin and oil red-0, they found fat and bone marrow emboli to the lungs in all animals (mean 0.91 emboli/mm^2). They assert, based on the binomial distribution revealed by their findings, that greater than 89% of intraosseous infusions will result in fat and bone marrow emboli to the lung. These animals received a manual bolus of drug followed by a 5 ml normal saline flush, with no record of the intraosseous pressure. As Welch et al. demonstrated, rapid infusions of 5 ml can increase intraosseous pressure six to eight times above baseline values, which may be responsible for the high occurrence

of fat and bone marrow emboli. Importantly, during the four hours of monitoring following infusion, there were no significant ventilation-perfusion abnormalities. This suggests that while fat and bone marrow emboli may result from intraosseous infusion they are likely not of clinical significance.

Further studies to determine the factors associated with pulmonary fat emboli were conducted on piglets.[67] Fluids were injected at rates up to 300 ml/hour and infusion pressure up to 300 mm Hg. Fat droplets were present in blood samples indicating embolization from the marrow cavity and fat emboli were identified in 30% of lung specimens. However, there was no consistent relationship between the presence of fat droplets and pulmonary fat emboli, and the presence of fat emboli in the pulmonary parenchyma seemed independent of the method of intraosseous infusion. An editorial by Byrick asserts that the clinical relevance of fat emboli remains unclear.[68] He comments that three factors interact to form fat emboli: the presence of open blood vessels in the marrow cavity, an elevated intramedullary pressure, and the presence of disrupted marrow contents at the time intraosseous pressure is raised. Thus while intraosseous infusions may lead to intravascular embolization of fat, the burden in the pulmonary vasculature may be lower than a threshold necessary to show clinical signs of pulmonary fat embolism. Furthermore, Harris, et al. calculated the lethal embolization of marrow fat to be 0.9 ml/kg body weight based on intravenous fat injection into a rabbit.[32]

Intra-Calvarial Infusion System (ICIS)

Intraosseous infusions have been performed in animal models into the tibia (proximal and distal), sternum, iliac crest, femur, and humerus. These sites have also been used in clinical studies, as have the clavicle and calcaneus. To date, the absorptive capacity of the skull has never been examined. While early studies stressed the importance of a vascular marrow cavity for fluid absorption, successful infusions into the calcaneus disputed this belief.[38] Intra-calvarial infusions present the additional challenge of accessing the vascular diploic space. The thickness of the outer table of the skull

varies between 3 mm and 6 mm, while to the diploic space is approximately 3 mm to 4 mm and the inner table only 1 mm thick. Percutaneous intraosseous needles present the risk of penetrating through the entire skull, violating the inner table and potentially injuring the underlying brain. Therefore, surgical drilling through the outer table under direct vision is the safest, most effective technique to access the vascular diploë. The human skull has a rich blood supply and drains via emissary and diploic veins into the deep dural sinuses. The pressure within these venous sinuses is essentially zero, suggesting that the intraosseous pressure limiting the resistance to infusion will similarly be very low.[32]

The clinical experience of intraosseous infusion indicates that long bones with a medullary cavity can effectively absorb medications and fluids at rates between 0.4 ml/min and 150 ml/min (24-9000 ml/hour) with few risks or complications. The purpose of studying the absorptive capacity of the calvarium is to develop an intra-calvarial infusion system suitable for the diversion of cerebrospinal fluid (CSF) for the treatment of hydrocephalus. CSF is produced at a constant rate of approximately 20 ml/hour in adults but somewhat less in children. Normally, the intracranial pressure (ICP) provides the driving force for CSF absorption at the arachnoid granulations into the dural sinuses. In hydrocephalus, there is an obstruction to the circulation and absorption of CSF leading to fluid retention and increased intracranial pressure. By diverting CSF to the vascular diploë, we can utilize the ICP to drive fluid indirectly into the dural channels and dural sinuses thus recreating the physiologic pathway for CSF absorption.

CHAPTER TWO
MATERIALS AND METHODS

General Materials

Central venous catheter

Infusion tubing

Suture

Heparinized saline

Three-way stopcock

Vacutainers

Needle-less blood collection equipment

Aspiration Pump

Camino ICP monitor

Infusion device

- Tap
- Self-tapping screws

Hand twist drill with 13/64" drill bit

Infusion tubing

Syringes

Infusion Pump

Surgical Equipment

Scalpel

Periosteal elevator

Retractors

Infusion Fluids

D50W

Technetium 99^{m}

10% FITC-Dextrans

Methods

Numerous animal models have been used to study intraosseous infusion. Previous studies investigated the physiologic response to infused fluids or medications through long bones with a well developed medullary space, most often the distal or proximal tibia. These studies investigated the usefulness of intraosseous infusion as compared with standard vascular infusions. Other studies investigated the safety of intraosseous infusion, both on the histological development of the bone, as well as complications related to such infusions. Animal experiments in dogs, goats, rabbits, and pigs have yielded valuable information regarding the safety and efficacy of intraosseous infusion. The past success of intraosseous infusions in clinical medicine, led to the idea of studying the absorptive capacity of the skull for the specific purpose as a site for the diversion of cerebrospinal fluid in the management of hydrocephalus.

Multiple experiments were necessary to direct the development of an effective intraosseous infusion device for delivery of fluids into the calvarial diploë. We studied the physiologic response to infused tracers in a dynamic pig model. In the literature, the pig was the most common animal model and previous trials in our lab with dogs, neonatal, adolescent, and adult pigs indicated that adult pigs would be most successful. Three different tracers were used during the evaluation of intraosseous infusion in the pig. Glucose, Technetium 99^{m}, and FITC-dextran infusions each provided valuable information, and adjustments were made throughout the course of this research. There was an evolution of the infusion device over the duration of the infusion studies as problems were encountered and considerations for the transferability of this technique to human skull infusions were discussed. Finally, human autopsy infusions were necessary to evaluate the venous drainage properties of the human skull to direct the development of the most appropriate infusion device.

Infusion Devices

Specific intraosseous infusion devices suitable for skull infusion were developed. Two designs were used in this study. First, a screw type infusion device (12 mm long, 5 mm external diameter, 3 mm internal diameter) with four side holes and a single end hole was used for the glucose injection studies (Figure 2-1). Following reflection of the scalp and stripping of the periosteum, a 13/64" drill bit was used with a hand twist drill to create a 15 mm deep burr hole through the outer table into the diploic space of the skull. Care was taken to ensure the integrity of the inner table, to prevent extravasation of blood into the epidural space. This hole was then pre-tapped by hand prior to placement of the screw type infusion device. A silicone gasket was used to improve the seal at the interface between the infusion device and skull. The infusion device was tightened using a hex-wrench until the gasket was deformed between the device and the skull. The trabeculated bone of the pig skull is softer than the human skull. It was difficult to secure the infusion device tightly and prevent leakage of infused fluids back up along the threads of the tapped burr hole even with the silicone gasket. This was one reason for changing the design of the infusion device for later experiments.

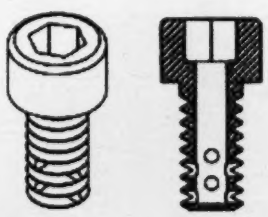

Figure 2-1. Screw-type infusion device. A 15 mm deep burr hole was drilled into the calvarial diploë, then hand tapped to allow placement of the infusion screw. A silicone gasket improved the seal at the interface between the skull and infusion device. Four side-holes along the shank of the screw increased the relative surface area for infusion of fluid.

The second limitation of the screw-type infusion device was revealed during autopsy infusions. During placement of the infusion device into the first human skull at

autopsy, the inner table of the skull was violated and fluid was infused into the epidural space. This being the most important complication to avoid, future infusions were delayed until a manifold style infusion device was developed. Two designs were developed. The first was a rectangular infusion manifold that required drilling of a thin trough into the calvarial diploë. Trials of preparing the trough and securing the infusion manifold to dried skull bones proved difficult. A round infusion manifold enabled simple preparation of a twist drill burr hole to access the diploic space of the skull for intraosseous infusion. This manifold style infusion device (5 mm aperture), was secured to the skull using six self-tapping screws (Figure 2-2), again using a silicone gasket to improve the seal at the interface with the skull.

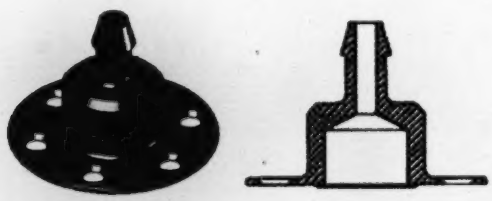

Figure 2-2. Manifold-style infusion device. Six self-tapping screws were used to secure the device to the outer table of the skull. A silicone gasket improves the seal at the interface with the skull.

Using the same 13/64″ bit and hand twist drill, a 10 mm deep burr hole was created through the outer table of the skull into the calvarial diploë. No tapping was required for securing this device. Care was taken to ensure no air was entrained into the richly vascular diploë by using continuous irrigation through and around the infusion device while securing it in place. The previous intraosseous literature, as well as our early experience, indicated that exposure of the vascular channels of the skull sometimes led to their occlusion. To maximize the absorptive capacity of the skull it was important to prevent the occlusion of the diploic channels.

Experimental Animals

Acute animal experiments, investigating the physiologic response to infused tracers in 14 crossbred adult pigs (40-56 kg), were approved by The Animal Care and Use Committee at the University of Alberta. All porcine infusion experiments took place in the Surgical Medical Research Institute animal operating room. Given the specific nature of this study, adult pigs weighing at least 40 kg were needed such that the skull was sufficiently ossified to drill into the trabeculated diploë and secure the infusion device. All animals had a central venous access line inserted into the left or right femoral vein to allow frequent blood sampling to measure the physiologic response to infused tracer.

All animals were housed and raised at the University of Alberta Animal Care Facility until they were the appropriate age and weight. The animals were transferred to the Surgical Medical Research Institute the evening before the experimental procedure and fasted overnight. Animals were pre-sedated using Ketamine (20 mg/kg) and Atropine (0.05 mg/kg) by intramuscular injection, then endotracheally intubated and maintained under general anaesthesia using 2-3% isofluorane for the duration of the study. Initially, the animals were positioned prone with the inguinal region cleaned with a betadine scrub for placement of a central venous catheter. A 10 cm incision was made immediately below the inguinal ligament, followed by dissection through the subcutaneous and deep tissues to expose the femoral vessels. The femoral sheath was opened and the vein separated from the artery. Care was taken to protect and preserve branches of the femoral vein as the vessel was skeletonized. Once the femoral vein was prepared, a 2-0 silk suture was passed around the distal aspect of the vessel and tied tightly to occlude venous return and gain control of the vein. A second 2-0 silk suture was passed around the vein proximally. A 16 gauge, 133 mm indwelling central venous catheter (BD Angiocath – Becton Dickinson Infusion Therapy Systems Inc., Sandy, Utah 84070) was placed in the left or right femoral vein in all animals to allow frequent serum sampling of infused tracers. The proximal

suture was then tightened around the vessel and catheter, securing the catheter in place. Venous blood return from the catheter confirmed placement in the central circulation. The central venous catheter was connected to silastic infusion tubing with the addition of two three-way stopcocks. The three ports of the proximal stopcock connected the tubing from the central venous catheter, an infusion line, and a vacutainer attachment. The distal three-way stopcock connected the infusion line with an intravenous solution of heparinized saline (allowing continuous gravity driven infusion), and an aspiration line (Figure 2-3). The aspiration line passed through a peristaltic pump which allowed aspiration of venous blood at a continuous rate. The three way stopcock was turned to exclude the aspiration line, and heparinized saline (1,000 I.U./L) was infused continuously through the femoral line to prevent venous thrombosis while the intraosseous infusion site was being prepared. The inguinal incision was then closed and the exiting central venous access line sutured to the skin to prevent dislodgement. During infusion experiments, the distal three way stopcock was turned to exclude the infusion of heparinized saline, and allow continuous aspiration of blood using a peristaltic pump. Needle-less vacutainer tubes were used to enable sampling of venous blood from the femoral line every 15 seconds while blood was continuously aspirated. This setup was necessary to study the rapidity with which tracers injected into the skull were distributed to the central circulation.

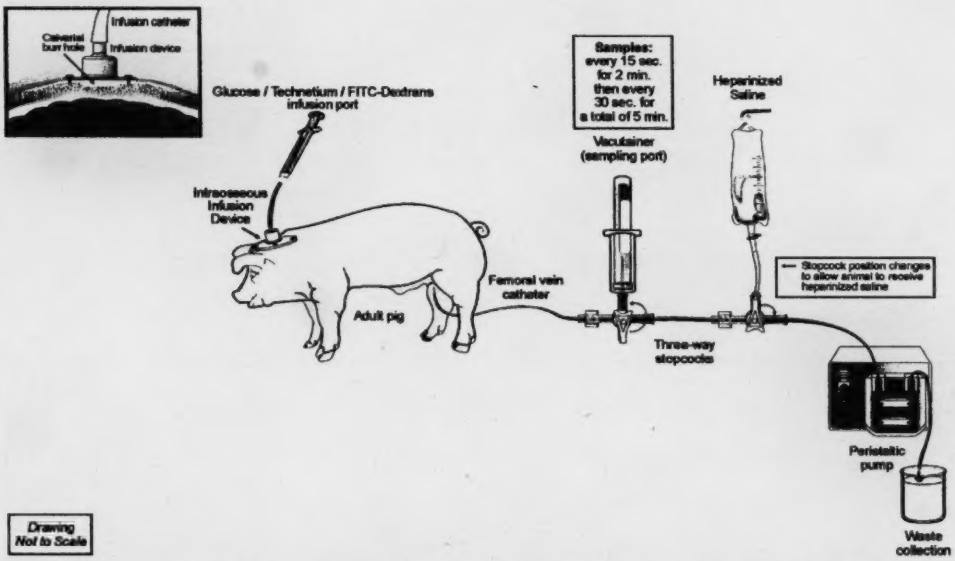
Infusion catheter
Calvarial burr hole
Infusion device
Glucose / Technetium / FITC-Dextrans infusion port
Samples: every 15 sec. for 2 min. then every 30 sec. for a total of 5 min.
Heparinized Saline
Vacutainer (sampling port)
Intraosseous Infusion Device
Femoral vein catheter
Stopcock position changes to allow animal to receive heparinized saline
Adult pig
Three-way stopcocks
Peristaltic pump
Waste collection
Drawing Not to Scale

Figure 2-3. Schematic representation of the experimental setup. The infusion pump used for continuous infusions and the parenchymal intracranial pressure monitor are excluded for simplicity.

With the central venous access line in situ, we turned the animal supine with the head supported at the end of the operating table. Placement of the intraosseous infusion device was by direct surgical exposure using a midsagittal linear incision through the scalp and subcutaneous tissues to the periosteum. The periosteum was reflected until the cranial sutures could be identified over the flat parietal surface of the skull. The last four animals had an OLM intracranial pressure monitor (Integra Neurosciences, Plainsboro, N.J. 08536) inserted into the contralateral or ipsilateral brain parenchyma prior to placement of the intraosseous infusion device. Using the included drill bit, a burr hole was drilled through the skull into the epidural space immediately posterior to the coronal suture. The dura was then opened to allow passage of the intracranial pressure monitor into the brain parenchyma. This was connected to a Camino V420 Monitor (Camino Laboratories, San Diego, CA 92121) for continuous measurement of the intracranial pressure. By inserting an intracranial pressure monitor, we were able to simultaneously measure the ICP during continuous intraosseous infusions.

At the conclusion of the study, animals were sacrificed using an overdose of Euthanyl (20 mL/45 kg) injected through the femoral venous line or intraosseous infusion device.

Tracers

Dextrose (D50W), Technetium 99^m, and fluorescein labeled FITC-dextrans were used to study the absorptive ability of the skull. Clinically, the intravenous injection of D50W leads to the rapid elevation of serum glucose. To study the response to injected dextrose, 20 ml of D50W was injected into the skull through the intraosseous infusion device in six experimental animals, and into the ear vein in the control. An early infusion of 50 ml D50W required two minutes due to the resistance through the bone. This slow infusion time limited the ability to determine the rapidity with which fluid is absorbed into the central circulation, thus 20 ml was found to be a more appropriate volume. Serum glucose was measured from the femoral vein every 15 seconds from time zero for the first two minutes, then every 30 seconds thereafter to follow the systemic response to this injection of dextrose. Serum blood glucose was measured using an YSI 2300 STAT plus glucose analyzer (YSI, Yellow Springs, Ohio 45387). Though infusion times were improved with the administration of 20 ml of D50W, the variability in the time required to inject this volume led to the investigation of alternate tracers as markers of absorption.

Initially, Technetium 99^m DTPA was chosen because of its common use as a radioactive marker for diagnostic imaging. Once absorbed into the general circulation, it is distributed diffusely into the plasma volume and excreted by the kidneys. Injection of only 2 ml to 5 ml was required to measure the rapid absorption of this marker in four experimental animals. However, radioactive handling precautions made this tracer somewhat difficult to use. Blood samples were drawn from the femoral venous access line every 15 seconds for the first two minutes, then every 30 seconds following the injection of Technetium 99^m through the skull infusion device. 200 µl blood samples were analyzed for radioactivity using a Minaxi Auto Gamma 5000 series gamma counter (Packard Instruments, Meriden, CT 06450).

Fluorescein labeled FITC-dextran (molecular weight 70,000) was injected through the intraosseous infusion device in eight experimental animals and the ear vein in the

control. Large molecular weight dextrans remain intravascular for up to 48 hours with little renal excretion. As a non-biologic marker, only 2 ml was needed to measure the rapid increase in serum fluorescence. Serum samples were taken from the femoral vein every 15 seconds from time zero for the first two minutes following injection, then every 30 seconds thereafter as previously. Serum fluorescence was measured using an FLx 800 fluorometric plate reader with excitation at 485 nm and emission at 535 nm (Bio-Tek Instruments Inc., Winooski, VT 05404).

Infusion Pressure Experiments

Following the tracer studies, 0.9% saline was infused at rates varying from 5-600 ml/hour utilizing an Asena automated infusion pump (Alaris Medical Systems, Basingstroke, RG22 4BS, UK) that simultaneously measured the infusion pressure necessary to deliver fluid at set rates. Continuous intraosseous infusions by this technique allowed assessment of the down-stream resistance to infusion in experimental animals and during human autopsy infusions.

Histological Examination

Developing an effective intraosseous infusion device for delivery of fluids into the calvarial diploë included studying the effect of drilling and tapping on the bony architecture of the pig skull. Methods for accessing the calvarial diploë included using a high-speed drill, hand twist drill, and hand twist drill plus curetting of the bony edges of the burr hole. The calvarium was removed at the conclusion of infusion studies, after additional investigative burr holes were drilled. The skull was sectioned using a high powered water-jet. Scanning electron microscopy of the sectioned skull and the walls of the drilled burr holes allowed investigation of the effect of drilling on the native architecture of the trabeculated diploë.

Specimens were fixed in 2.5% glutaraldehyde and 1% Osmium or in M Millonig's buffer for 2 hours at room temperature respectively. The samples were then

dehydrated in a graded series of ethanol solution, and critical-point dried in a CO_2 critical point dryer (Model CPD-100, Seevac Inc., Pittsburgh, PA). After mounting the specimens were coated with gold in a sputter coater (Edwards S150B, Edwards, West Sussex, England). Specimens were observed using a Hitachi S-2500 SEM (Hitach, Tokyo, Japan).

Human Autopsy Studies

To ascertain the potential for intraosseous infusion into the human calvarium, autopsy studies were designed to test the transferability of this technique to human skull systems. This involved developing an appropriate infusion device, identifying the path of venous drainage from the diploic space, and determining the resistance to infusion presented by the calvarial diploë. Intraosseous infusion into the human skull at the time of autopsy was approved by The Health Research Ethics Board at the University of Alberta Hospital. Following bicoronal reflection of the scalp, the periosteum was stripped posterior to the coronal suture and lateral to the sagittal suture. Using a 13/64" drill bit and hand twist drill, a burr hole was made through the outer table of the skull into the calvarial diploë. As with the early animal infusions, this hole was hand tapped and the screw type infusion was device was placed. The human skull, being much thinner than the pig skull, accommodated a burr hole only 5 mm in depth. The infusion screw, at 12 mm in length, was too long to achieve an adequate seal at the interface with the bone. In addition to leakage of infused fluids due to the poor seal, even careful preparation of the burr hole and placement of the infusion screw could not prevent penetration through the inner table. Subsequently, the manifold-style infusion device was used to avoid this complication. Injection of India ink was used to visualize the venous drainage from the diploë. Following the hand injection of ink, a syringe pump with down-stream pressure monitor was used to inject water at a continuous rate and measure the pressure required to inject water at set rates. Water was injected at rates between 5 and 200 ml/hour. Following the infusion experiments, the calvarium was removed as part of the autopsy and to allow

visualization of the under surface of the skull for extravasation of fluid into the epidural or subdural space.

CHAPTER THREE
HISTOLOGY

Intraosseous infusion into the medullary cavity of long bones has been performed using various types of infusion devices. Accessing the calvarial diploë, however, presents certain obstacles. One cannot easily insert a needle into the narrow diploic space of the skull especially with the brain located so closely beneath. Rather, burr holes must be drilled using a combination of direct visual guidance and surgical 'feel'. Clinically, burr holes are fashioned with either high speed drills or hand twist drills. Using hand twist drills, the compactness of the outer cortical bone can be felt. In contrast, the trabeculated diploë is looser and easier to drill. Upon reaching the inner cortical bone, the increased density is appreciated. Using high speed drills, the tactile feedback is limited, until the resistance is felt to diminish with penetration through the inner table. Maintaining the integrity of the inner table is the most important objective when developing an intraosseous infusion system into the calvarial diploë, since epidural extravasation of fluid could be a fatal complication.

The pig skull is considerably thicker than that in humans. This reduced the concerns regarding penetration of the inner table during porcine infusions. However, the pig skull is also more cartilaginous and the fine trabeculae of the cancellous diploë more fragile. These findings were thought to play a role in the variability of resistance to intraosseous infusion, which will be discussed later. As such, we sought to determine which technique for accessing the calvarial diploë would be least disruptive to the native architecture of the skull.

Various techniques were used to access the calvarial diploë; a high speed drill, a hand twist drill, and a hand twist drill followed by sharp curettage to remove any bone fragments and cleanly fracture the bone in an attempt to preserve the spaces between the trabeculae. Each of these techniques was assessed by scanning electron microscopy (SEM) to observe the effect of drilling methods on the trabecular structure of the bone. At the conclusion of the infusion experiments and after drilling

additional burr holes by various techniques, the calvarium was removed. A water jet cutter was used to create precise cross-sections of the calvarium to demonstrate the native architecture of the cancellous diploë as well as the bony disruption associated with drilling.

Venous bleeding from the skull gives an indication of the ability of the skull to absorb infused fluids. Using the hand twist drill, we found slow but continuous bleeding from the vascular diploë. Continuous irrigation with heparinized saline improved bleeding from the skull by limiting clotting associated with exposure to air. This was an important finding since the pig forms thrombus very quickly. Curetting the drilled walls and depth of the burr hole led to decreased bleeding, though this may in part have been related to some air exposure. An interesting finding was the absence or very poor bleeding following high speed drilling. By contrast, we routinely find vigorous bleeding in human burr holes drilled with a high speed drill during craniotomies. Venous bleeding was best preserved by using a hand twist drill with continuous irrigation to create the burr hole, and ongoing irrigation during placement of the infusion device.

Sections of the pig skull clearly demonstrate the destruction of the trabecular structure caused by different drilling techniques. Figure 3-1 shows the structure of the porcine skull. The outer cortex is densely packed and offers little absorptive potential while the inner cancellous diploë is richly vascular. Venous blood flows through the channels between bony trabeculae, eventually finding an emissary or diploic vein which returns blood to the central venous circulation.

Figure 3-1. Scanning Electron Micrograph of the sectioned surface of the porcine skull. The dense cortical bone can be seen at the top of the image, with the vascular cancellous diploë beneath. Maintaining the natural trabeculated structure of the bone is important to reduce the resistance to intraosseous infusion.

Early infusion experiments were conducted using the screw-type infusion device, which required hand drilling and tapping the burr hole prior to placement of the infusion device. The process of twisting the sharp tap to create threads for the infusion screw smeared bony fragments and debris into the channels of the cancellous bone (Figure 3-2 and 3-3). This blocked the absorption of infused fluids and led to an increased resistance to infusion.

Figure 3-2. Scanning Electron Micrograph of the inner surface of the burr hole. Note the tapped threads that were needed for placement of the screw-type infusion device. Even at this magnification, the disruption to the normal cancellous architecture is obvious.

Figure 3-3. Higher magnification SEM of the threaded burr hole. Bone fragments have been pressed into the cancellous spaces creating an obstruction for the absorption of infused fluids as well as limiting venous bleeding from the skull.

Needing to minimize the resistance to infusion, we sought alternative techniques for accessing the calvarial diploë. This involved developing a manifold-style infusion device as well as investigating alternative drilling techniques. We observed very little, if any, venous bleeding from the skull when using the high speed drill to create the burr hole. As shown in Figure 3-4, the high speed drill disrupts the fine bony trabeculae and packs the diploic spaces restricting blood return and fluid absorption.

Figure 3-4. SEM of a burr hole made by the high speed burr. The smooth surfaces of the burr hole are created by the smearing of bone fragments into the cancellous spaces of the bone. The cut surface of the skull demonstrates the native architecture.

Borrowing from geotechnical knowledge and experience drilling through various porous and solid materials, we investigated the effects of bone "smearing" caused by high speed drilling. We investigated the ability of a hand twist drill, with or without sharp curettage, to preserve the trabecular structure of the diploë. Twist drilling alone, with continuous irrigation to prevent thrombus formation or air occlusion, created a burr hole which preserved to greatest extent the open cancellous nature of the diploë (Figure 3-5 and 3-6). We also observed ongoing venous bleeding from the skull

during preparation of the infusion site in this manner. Noting the fine debris that can be seen in the scanning electron micrographs, we attempted to remove this obstruction by sharp curettage. We were surprised that rather than removing debris and creating sharply fractured and open trabeculae, we actually packed debris more firmly within the bone further obstructing the sites of fluid absorption (Figure 3-7).

Figure 3-5. SEM of the inner surface of a burr hole made using a hand twist drill. The bony trabeculae are preserved though there is debris partially obstructing the vascular channels

Figure 3-6. Higher power SEM of the same burr hole as Figure 5. Notice how the bone fragments have settled within the vascular channels of the cancellous bone.

Figure 3-7. SEM of the wall of a curetted burr hole. Some preserved bony trabeculae can be seen in the upper right hand area of the image; however, the smearing of bone fragments into the cancellous bone in obvious. Rather than opening the spaces between trabeculae, curetting the bone packed debris into the vascular spaces.

CHAPTER FOUR
GLUCOSE STUDIES

During the development of the calvarial infusion device and refinement of our technique for accessing the cancellous diploë, we also investigated a number of tracers to study the physiologic response to calvarial infusion. D50W is commonly used in clinical practice to increase serum glucose in hypoglycemic patients. Glucose solutions have also been used in animal intraosseous infusion studies to treat insulin induced hypoglycemic seizures. In our first dynamic intraosseous infusion study, using the screw-type infusion device, we injected 50 ml D50W into the calvarial diploë. It took two minutes to inject this volume of dextrose due to the resistance to intraosseous infusion. Serum glucose was measured every 30 seconds starting one minute following the completion of the dextrose injection (Figure 4-1). The baseline serum glucose was 70 mg/dl which increased to 171 mg/dl at 180 seconds and remained elevated at more than double the baseline glucose out to ten minutes. With the long infusion time and delay before the first measurement of serum glucose, we may have missed an earlier peak of serum glucose.

This first infusion demonstrates the ability of the skull to absorb fluids into the systemic circulation; however, the prolonged time required for injection of this volume of D50W limits our ability to comment on the rapidity with which fluid is absorbed. For subsequent infusions, we decreased the volume of D50W injected to 20 ml.

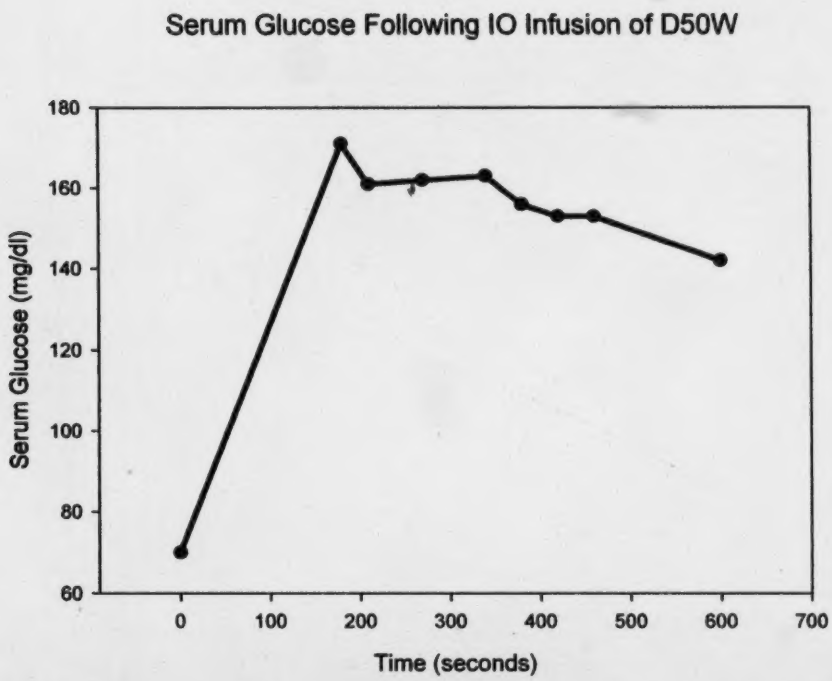

Figure 4-1. Serum glucose following intraosseous injection of 50 ml D50W. The time required for injection was two minutes. Serum glucose was measured at baseline and every 30 seconds beginning three minutes after the start of infusion.

Six crossbred adult pigs weighing 46 – 56 kg (mean 51.5 kg) were used to study the physiologic response to intraosseous injection of 20 ml D50W into the calvarial diploë. The screw-type infusion device was used for the first four infusions while the manifold style infusion device was used for the last two infusions and the negative control. The time required for injection ranged from 16 seconds to 86 seconds (mean 43.17 seconds). Serum glucose was measured at time zero, then every 15 seconds for the first two minutes and every 30 seconds thereafter for a total of five minutes.

There is an elevation in serum glucose within 45 seconds and a peak within 2 minutes in most animals followed by a plateau (Figure 4-2). The pig's insulin response to dextrose infusion limits the elevation in serum glucose and leads to a consistent plateau level following intraosseous injection. The variability of baseline glucose as well as the inconsistent time required for infusion led to irregularity in the slope of

the glucose response curves for different animals. The results from certain animals deserve specific comment. The two pigs with the highest baseline serum glucose showed the smallest elevation in serum glucose following dextrose infusion. These particular animals also had the fasted and slowest infusion times at 16 seconds and 86 seconds respectively and both were with the screw-type infusion device. The infusion that was completed in 16 seconds had minimal resistance and we were concerned that there was a violation of the inner table with epidural extravasation of dextrose. Following the infusion studies, the skull was removed and confirmed the placement of the screw-type infusion device through the inner table. The epidural extravasation of dextrose limited the amount absorbed by the skull into the general circulation and delayed the elevation of serum glucose. The animal with the slowed infusion of dextrose over 86 seconds, showed a similarly slow increase in serum glucose. The remaining four animals had more consistent glucose response curves.

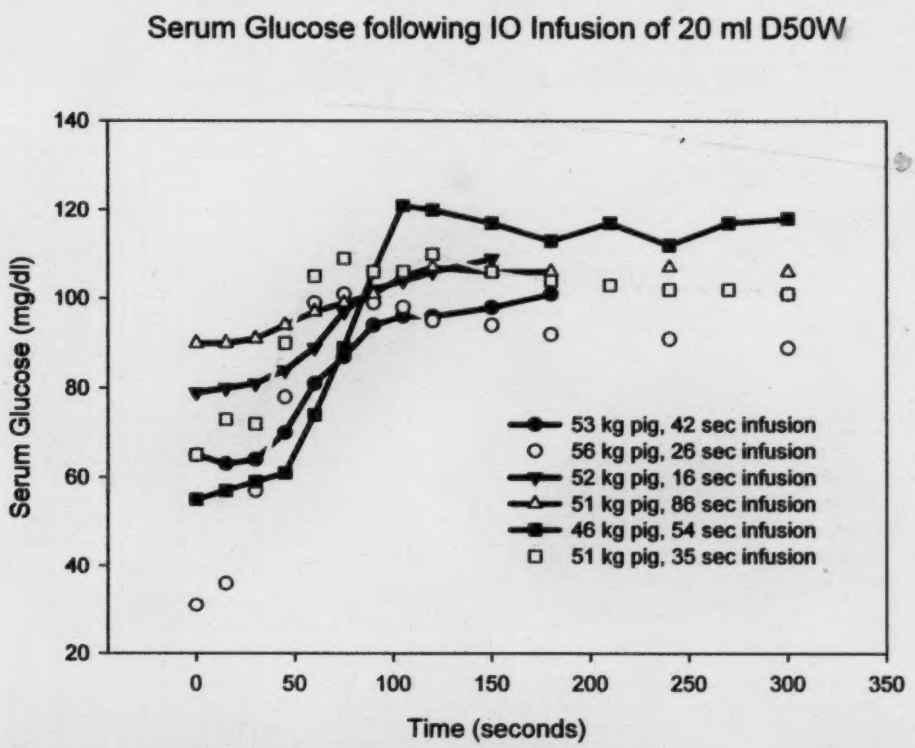

Figure 4-2. Serum glucose following calvarial infusion of D50W. The wide variability of baseline glucose contributes to the irregular glucose uptake curves. The more consistent plateau glucose likely reflects the reliable insulin response of the pig.

To compare the absorption of dextrose infused into the calvarial diploë with that delivered directly into the venous system, we injected 20 ml D50W into the ear vein of a control pig. The time required for intravenous injection was 26 seconds as compared with the average intraosseous infusion time of 43.17 seconds. As a result, the elevation of serum glucose was faster for direct intravenous injection (Figure 4-3).

The plateau level of serum glucose was similar to that following intraosseous infusion owing to the pigs' insulin response and indicates a complete absorption of dextrose infused into the calvarial diploë. To demonstrate that the elevation in serum glucose was not due to some other factor, we conducted a negative control in which 20 ml saline was injected into the calvarium through the infusion device. There was no change in serum glucose associated with this injection.

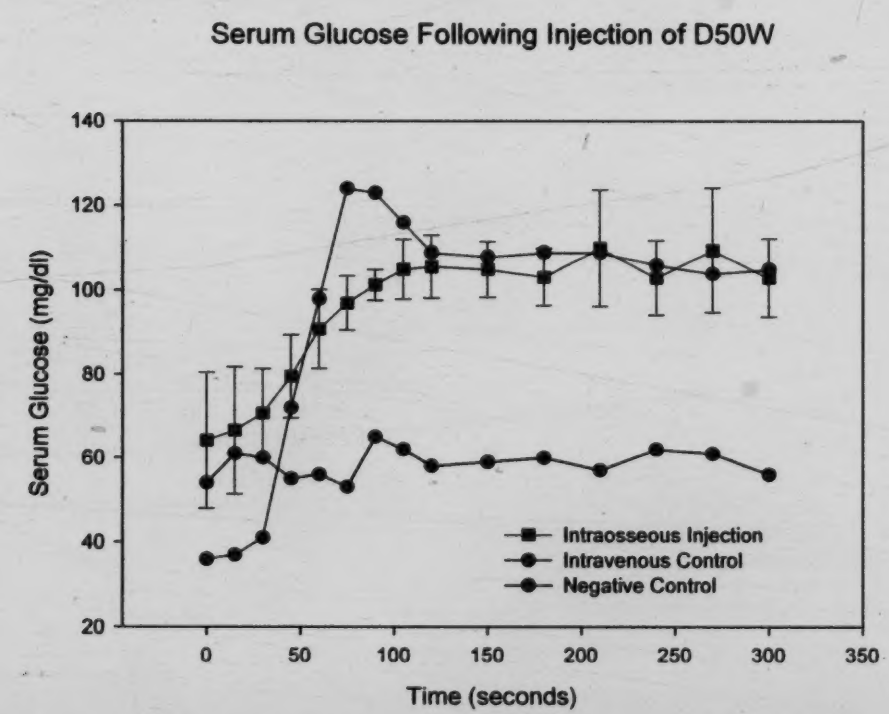

Figure 4-3. Elevation of serum glucose following intraosseous infusion of D50W as compared with direct intravenous delivery. The more rapid elevation of serum glucose following intravenous injection is due to the quicker injection time. Note the similar plateau level of serum glucose that indicates complete absorption of dextrose infused into the calvarium. The negative control, shown in black was the change in serum glucose following intraosseous infusion of saline.

These glucose infusions clearly demonstrate the absorptive capacity of the skull; however, there were a number of limitations encountered during the experiments. The first was the prolonged infusion time required to infuse large volumes of D50W which prompted the change in experimental procedure to inject 20 ml rather than the original 50 ml. While this improved the delivery time and enabled us to demonstrate a rapid systemic uptake, it was still much slower than delivery directly into the ear vein making comparison between intraosseous infusion and intravenous injection difficult. This was in part due to the high resistance to infusion encountered using the screw-type infusion device in the porcine skull. Future experiments, using the manifold style infusion device and small volume tracers, better demonstrate the rapid absorption into the general circulation from the calvarial diploë. These will be discussed in subsequent chapters. The other limitation of dextrose infusion is the pig's robust insulin response to elevations in serum glucose. Even with a large variability in baseline serum glucose (31-90 mg/dl), the peak serum glucose following administration of 20 ml D50W was tightly controlled between 101 mg/dl and 124 mg/dl. Injection of 50ml D50W did lead to a larger elevation of serum glucose, however we needed to strike a balance between injection time and systemic uptake.

While limitations existed in these experiments, the elevation in serum glucose following intraosseous infusion of D50W was similar to that following direct intravenous injection. This demonstrates for the first time the absorptive capacity of the cancellous diploë of the skull substantiates our technique to safely access the calvarial diploë for intraosseous infusion.

CHAPTER FIVE
TECHNETIUM-99^{M} STUDIES

One of the most common isotopes used in medicine, metastable technetium-99 (Tc-99m), bound to diethylenetriaminepentaacetate (DTPA) was used in five animals to confirm the absorptive capacity of the porcine skull. Tc-99m decays to Tc-99 primarily by gamma emission and has a half-life of approximately six hours. Being an inorganic radioactive isotope, very small quantities can be injected and detected by a gamma counter. Serum samples were collected from the femoral vein, using the same technique as previously described, allowing frequent analysis of gamma activity. Between 2 ml and 5 ml Tc-99m DTPA was injected into the calvarial diploë through either the screw-type or manifold style infusion device. Even with this smaller volume infusion, the time required for injection varied from 8 seconds to 35 seconds (mean 16.8 seconds). The measured gamma activity was determined and corrected for circulating blood volume. The blood volume of crossbred adult pigs is 56 ml/kg. Tc-99m DTPA is freely filtered across the glomerulus and excreted in the urine. This removes technetium from the circulating volume continuously, limiting the serum gamma activity.

The first two infusions were performed using the screw-type infusion device. In both cases, the screw was secured in the skull without violation of the inner table so we were sure there was no extravasation of fluid into the epidural space. However the seal of the infusion device to the skull was poor allowing leakage of Tc-99m DTPA. This was confirmed by assessing the gamma activity of a gauze pad which was wrapped around the infusion device at its interface with the skull. As was found with the glucose infusions, there was inconsistent resistance which may have been due to variable smearing of the bone within the burr holes or may relate to the unreliable seal of the screw-type infusion device to the skull. The results demonstrate that the serum gamma activity from these first two infusions is poor, reaching only 4% and 12% of the injected dose (Figure 5-1). This is in part due to the excretion of Tc-99m DTPA in the urine, but more likely due to leakage from the infusion device.

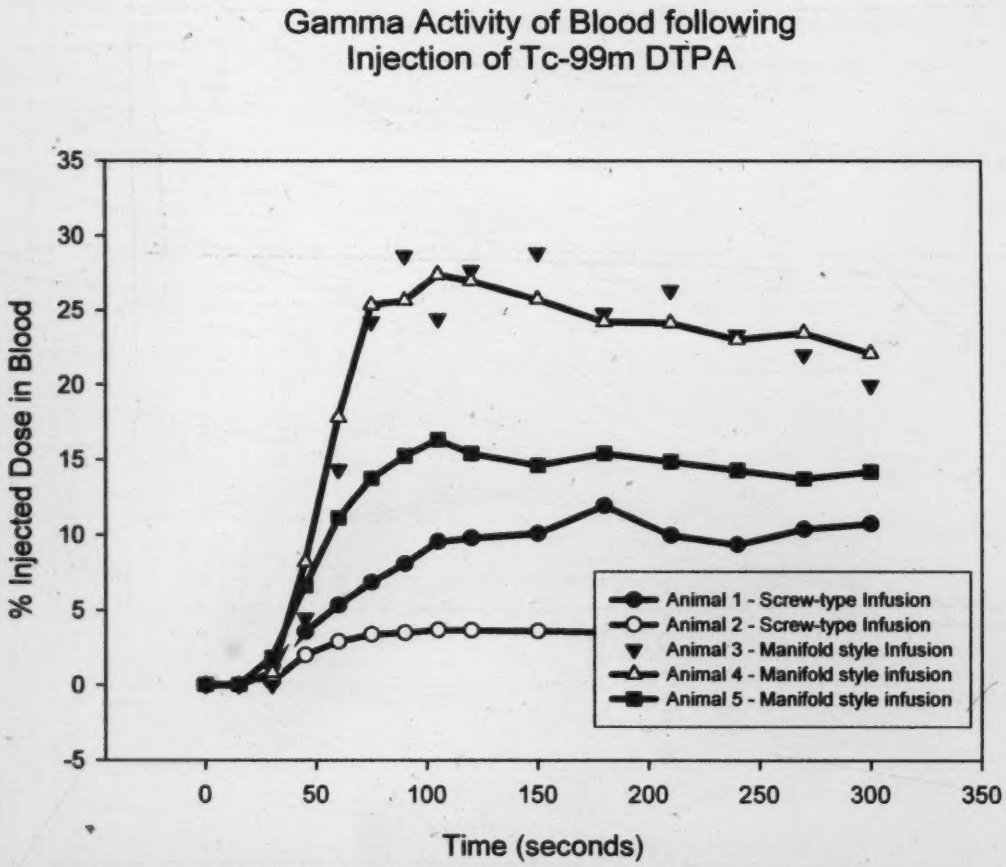

Figure 5-1. Gamma activity in blood following intraosseous injection of Tc-99m DTPA. The % injected dose is based on the activity of the serum samples at each time point as compared with the activity of the original sample of technetium. Tc-99m DTPA is freely filtered across the glomerulus and collects in the urine, limiting the activity in the circulating blood volume. The first two animals (red and green data) received intraosseous infusion through the screw-type infusion device. The lower gamma activity likely represents leakage of Tc-99m DTPA from the site of infusion. The final animal (pink data) also shows a lower gamma activity as compared with the two previous manifold style infusions (yellow and blue data), again due to leakage of infusate from the site of infusion.

As the dynamic infusion studies were conducted in parallel with changes in the infusion device and improvement in the technique for accessing the calvarial diploë, the last three technetium infusions were performed using the manifold style infusion device. The manifold style infusion device was secured to the skull using six self-tapping screws and a silicone gasket to improve the seal. In the second manifold infusion experiment, fluid could be seen leaking from the skull through emissary

channels. We slowed the injection to limit the leakage of technetium from the diploic space. In the first two manifold infusions, the gamma activity peaked at 29% and 27% which was much improved as compared to the earlier infusions using the screw-type infusion device (Figure 5-1). This is likely explained by the improved seal and diminished leakage at the interface between the infusion device and the skull.

The final infusion study using the manifold style infusion device yielded conflicting results. We noticed leakage of fluid from the securing screws around the perimeter of the manifold style infusion device. These screws may have penetrated through the outer table of cortical bone into the cancellous diploë creating a pathway for fluid to leak out resulting in diminished gamma activity.

As a non-physiologic marker, Tc-99m is useful for studying the intraosseous absorption of fluid. We were able to eliminate the concerns regarding the pigs' innate management and tight control of serum glucose. However, there are a number of limitations related to Tc-99m DTPA infusions. Access to the animal operating room was restricted to individuals certified to work with radioactive isotopes. Following infusions the operating room then had to be closed to other investigators for three days to allow the decay of Tc-99m. Finally, small leaks were difficult to identify given the small volumes infused and the colorless nature of the tracer. These leaks played a major role in the inconsistency of our results since the serum radioactivity is measured so easily with a gamma counter.

Overall, the steep uptake curves of serum gamma activity demonstrate the rapid absorption of fluid injected into the calvarial diploë into the general circulation. This confirms the results of the previous glucose infusions and strengthens our resolve that the skull has the capacity to absorb infused fluids rapidly into the venous system of the head and neck.

CHAPTER SIX
FITC-DEXTRAN STUDIES

Glucose infusions into the calvarial diploë established the absorptive capacity of the skull to physiologic solutions and demonstrated the communication between the vascular diploë and the general circulation. However, these studies were limited due to the large volume of D50W that needed to be injected in order to demonstrate a significant elevation in serum glucose. Technetium infusions confirmed the ability of the skull to absorb fluids into the systemic circulation, although small leaks were difficult to recognize leading to uncertain results. We needed another tracer that could be used to assess the rapidity with which fluid entered the venous system following intraosseous infusion into the calvarial diploë.

Fluorescein isothiocyanate dextrans (FITC-Dextrans) are valuable tracers in morphological studies because they can be visualized by both light and electron microscopy.[69] Dextrans are useful for physiologic studies because they are water-soluble, stable, and nontoxic.[70] Various molecular weight compositions of dextrans are available. Smaller dextran molecules with molecular weights less than 15,000 are freely filtered across the glomerulus and excreted in the urine, whereas larger molecules with molecular weights above 50,000 remain within the vasculature.[71] We used a D70 preparation with an average molecular weight of 70,000 (> 90 per cent of the molecules have a molecular weight between 20,000 and 140,000) to limit the amount cleared by the kidney during our infusion studies.

To evaluate the time required for intraosseous infusions to enter the central circulation, we injected 2 ml of 10% FITC-Dextrans through the manifold style infusion device of 8 crossbred adult pigs. As we refined our technique for accessing the calvarial diploë, we learned that the manifold style infusion device eliminated the risk of penetration through the inner table of the skull, lessened the leakage from the interface between the skull and the infusion device, and facilitated human calvarial infusions due to its ease of placement. We decided that the manifold style infusion

device should be used for all of the FITC-Dextrans infusions. Serum samples were collected every 15 seconds for the first two minutes following intraosseous injection of FITC-Dextrans, then every 30 seconds for a total of five minutes, as previously described. The 8 pigs ranged in weight from 40 kg to 59 kg (mean 50 kg). The time required for intraosseous injection of 2 ml FITC-Dextrans was between 5 seconds and 10 seconds in seven of the experimental animals. One animal had leakage from emissary channels in the skull distal to the infusion site and infusion was slowed to 35 seconds. The fluorescein is well visualized by its orange color and enabled us to recognize any leaks from the infusion device or the skull. During another infusion we identified a small amount of leakage from around the self-tapping screws. This likely resulted from penetration of the screws into the vascular channels of the cancellous diploë, allowing a small extravasation of fluid. The results demonstrate that in the two animals where leakage was identified there was a diminished elevation of serum fluorescence (Figure 6-1). There is a significant elevation of serum fluorescence by 30 seconds in four of the eight experimental animals and by 45 seconds in the remainder. The serum fluorescence peaks between 75 seconds and 105 seconds in all experimental animals followed by a plateau for the remainder of the study. All results were standardized by blood volume which is approximately 56 ml/kg for the crossbred adult pigs used in this study.

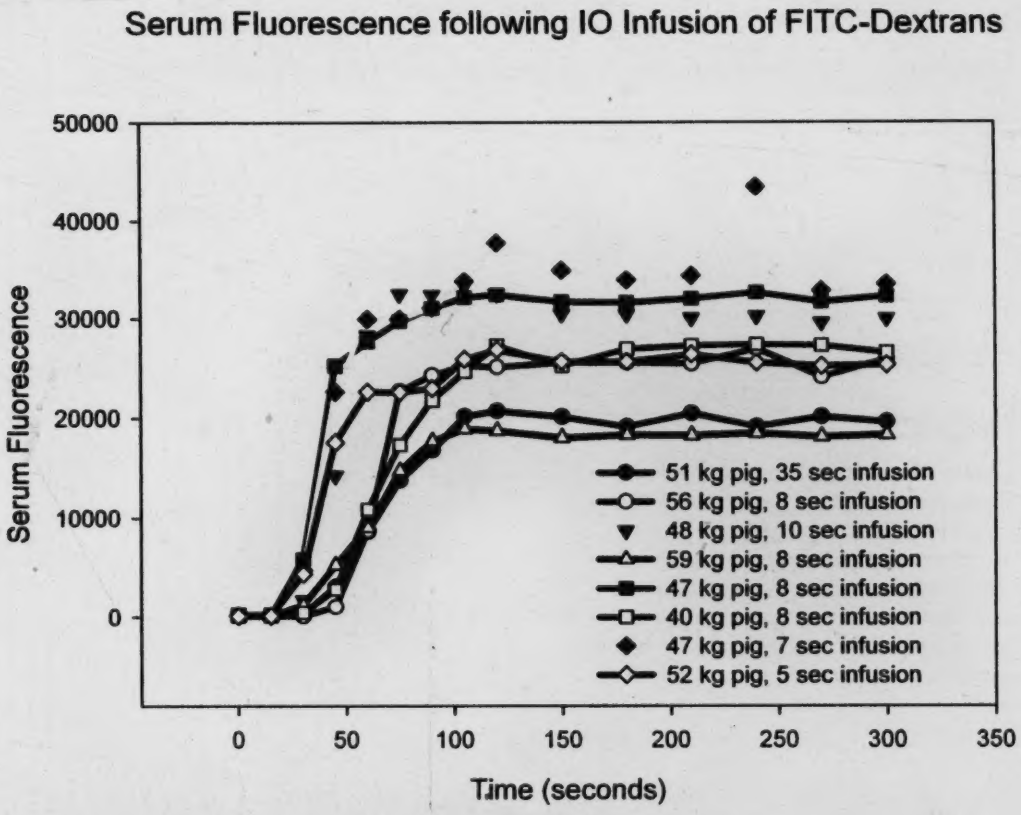

Figure 6-1. Serum fluorescence following intraosseous infusion of 2 ml 10% FITC-Dextrans in eight experimental animals. Individual animal weights and infusion times are indicated. The two animals that showed the smallest increase in serum fluorescence (red and blue data) both had complications related to the infusion. The rapid increase in serum fluorescence demonstrates the rapid delivery of fluid from the calvarial diploë to the central circulation.

To compare the central delivery of fluids injected into the calvarium with those injected directly into the venous system we injected 2 ml of 10% FITC-Dextrans into the ear vein of one control animal. The result from the one animal where the infusion was intentionally slowed to reduce leakage from emissary channels was excluded since this infusion was not consistent with the other intraosseous infusions. The infusion time for the remaining seven experimental animals was 5-10 seconds (mean 7.7 seconds). This compared with an infusion time of six seconds in the control animal. The collective data from the intraosseous infusions shows that fluids injected

into the calvarial diploë reach the central circulation as quickly as when injected directly into the venous system (Figure 6-2).

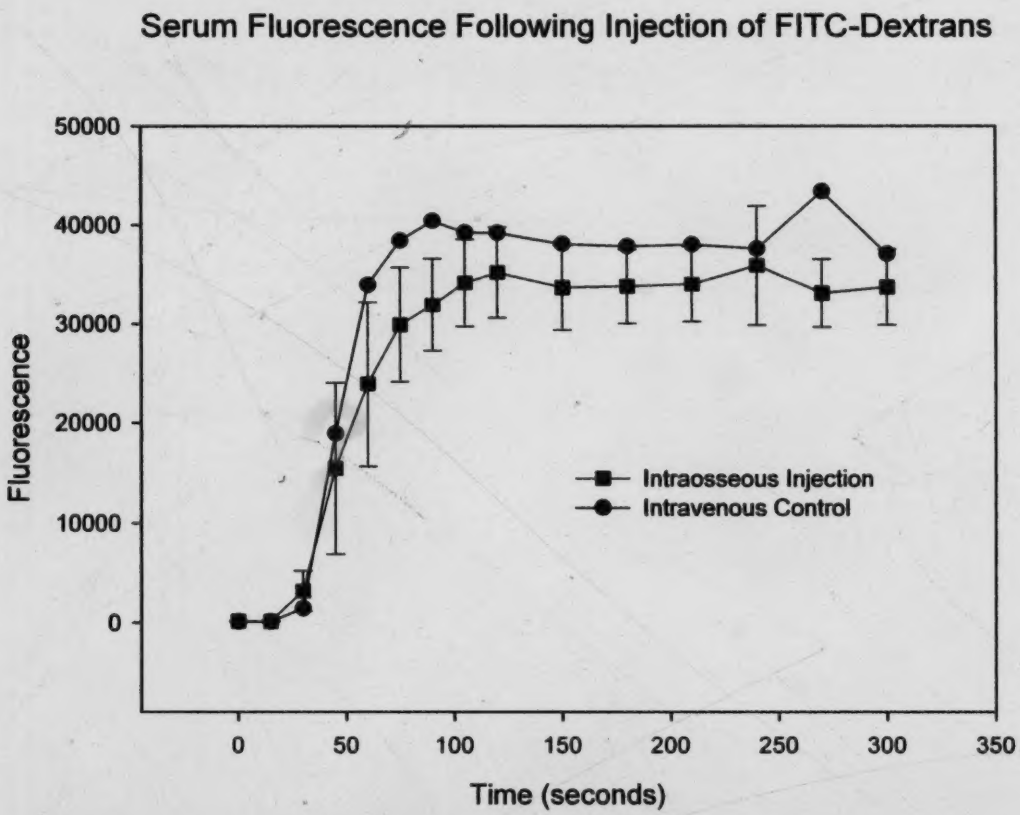

Figure 6-2. Increase in serum fluorescence following injection of FITC-Dextrans into the calvarial diploë in seven experimental animals (shown in green) as compared with direct intravenous injection in the control (shown in red). The time required for IO infusion of 2 ml averaged 7.7 seconds, while the control infusion into the ear vein took 6 seconds. The similar slope of the resulting curves demonstrates that fluid injected into the calvarial diploë is distributed to the central circulation as quickly as that injected directly into the venous system.

The slopes of the serum fluorescence curves of experimental animals and the control almost overlap demonstrating the similarity in central delivery. The similar plateau levels suggest that there is very little leakage from the manifold style infusion device or from the calvarial diploë and that all of the FITC-Dextrans reach the central circulation.

Intraosseous infusions of fluorescein into the calvarial diploë demonstrate the rapid delivery of fluids into the central circulation. As a non-biologic tracer, fluorescein uptake validates the results of dextrose and technetium infusions. The advantage of injecting a small volume tracer with the additional benefit of revealing any leakage from the infusion device make this tracer superior to those previously studied. We were able to control the rate of injection based on any evidence of leakage without the added constraints of working with radioactive tracers.

The infusion of 2 ml FITC-Dextrans in 5-10 seconds (12-24 ml/min or 720-1440 ml/hour) greatly exceeds the absorptive requirement for the clinical application of intraosseous diversion of CSF in the management of hydrocephalus. These infusions demonstrate the usefulness of the manifold style infusion device. With slower rates of infusion, and therefore lower pressure, there was no leak of infusate from the infusion device with rapid delivery of tracer to the central circulation.

CHAPTER SEVEN
INFUSION PRESSURE STUDIES

Cerebrospinal fluid (CSF) formation by the choroid plexus and ventricular ependyma is pressure independent. However, CSF absorption at the arachnoid granulations is pressure dependent. The normal driving force for CSF absorption is the difference between the intracranial pressure (ICP) and the venous pressure of the dural venous sinuses. Normal ICP varies between 10 and 20 mm Hg while the central venous pressure within the dural sinuses range between zero and 5 mm Hg. Ideally, an intraosseous infusion device for the diversion of CSF will recreate this physiologic resistance to absorption.

We conducted a series of infusion studies to measure the driving pressure required to infuse saline at set rates during porcine infusions and human autopsy infusions. All of the infusion pressure studies were performed using the manifold style infusion device. We found considerable variability in the resistance to intraosseous infusion as different techniques were employed to access the diploic space. For the early infusions the burr hole was prepared using a hand twist drill followed by curettage of the walls of the cancellous diploë. The infusion pressure necessary to drive infusion increased in a linear fashion as the rate of infusion was increased in each of the first two experiments; however, the infusion pressure at any given rate of infusion differed greatly (Figure 7-1).

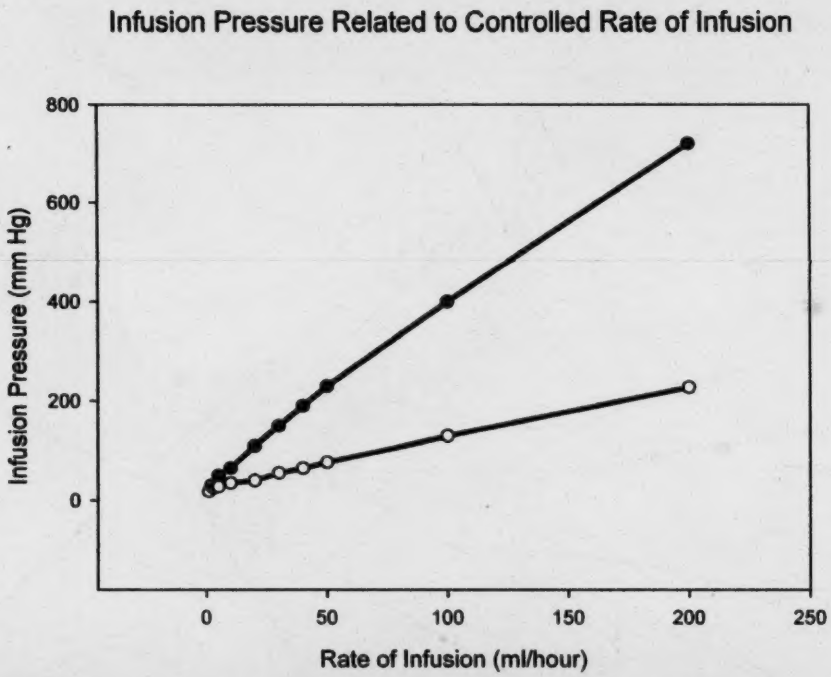

Figure 7-1. Early intraosseous infusion studies into the porcine skull using a hand twist drill and curette to access the calvarial diploë. The widely disparate results are likely due to the relative occlusion of vascular channels due to smearing of bone.

These results seemed to parallel our histologic observations of the burr holes, which demonstrated considerable smearing of bone by the sharp curette. The widely disparate results found in these early infusions can be explained by blockage of the cancellous channels of the calvarial diploë restricting the absorption of infused fluids. For the next infusion, we made the burr hole using the hand twist drill without curetting the walls. The rates of infusion were restricted to between 1 ml/hour and 40 ml/hour, which represents a more physiologic range. We were surprised to find the infusion pressure for any given rate of infusion to be even higher than the two previous infusion experiments (Figure 7-2). This challenged our hypothesis that the high resistance to infusion was due solely to the destruction of the trabeculated channels of the skull and led to a review of the intraosseous literature to determine what factors influence the resistance to infusion.

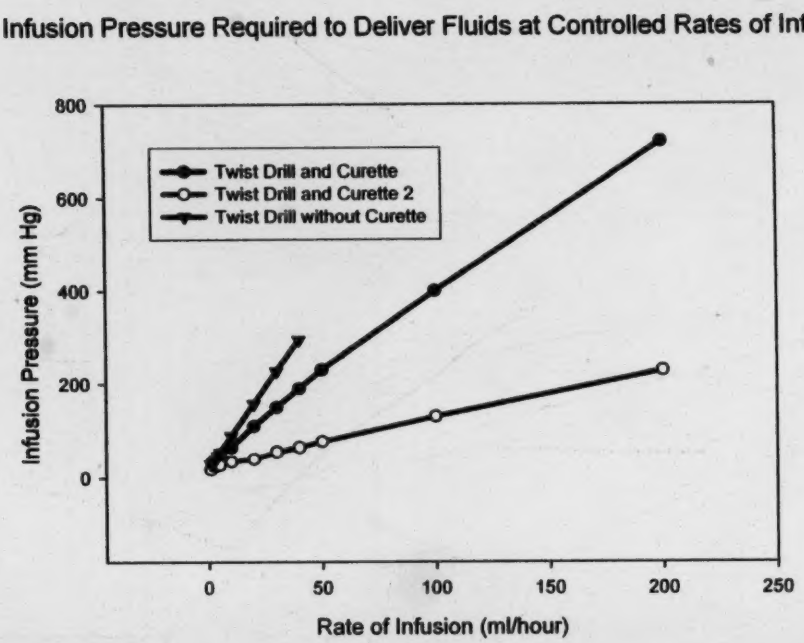

Figure 7-2. The resistance to infusion was even higher when a curette was not used to access the diploë. Factors other than bony smearing, such as thrombus formation, must also occlude the vascular channels.

Early reports indicating the success of intraosseous infusion describe techniques to maintain an adequate rate of infusion. Leandro Tocantins and colleagues advised swift placement of the intraosseous needle and rapid commencement of inward fluid flow through into the marrow space to avoid thrombus formation within the needle.[25, 32, 48] As our technique requires an open surgical access of the vascular diploë, there is the additional risk of clotting or "air-lock". To address these issues we modified our technique of preparing the burr hole and securing the infusion device. Firstly, we focused on preventing air entrainment at the infusion site by continuously irrigating heparinized saline while drilling the burr hole. We then infused heparinized saline through the infusion device while the screw holes were pre-drilled and the self tapping screws were tightened, thus securing the infusion device in place. This also provided us the opportunity to observe the increase in resistance to infusion as the infusion device was secured and sealed to the skull. Another feature of intraosseous infusion that was identified was a decrease in resistance following initial infusion of 20 to 30 ml.[24, 32] To address this issue, we continued infusing heparinized saline at

200 ml/hour until at least 20 ml had infused. We observed a considerable decrease in the pressure necessary to infuse this fluid during this period. By modifying the techniques of accessing the diploic space, securing the infusion device, and ensuring a continuous high flow infusion prior to conducting infusion studies, the resistance to infusion decreased dramatically (Figure 7-3).

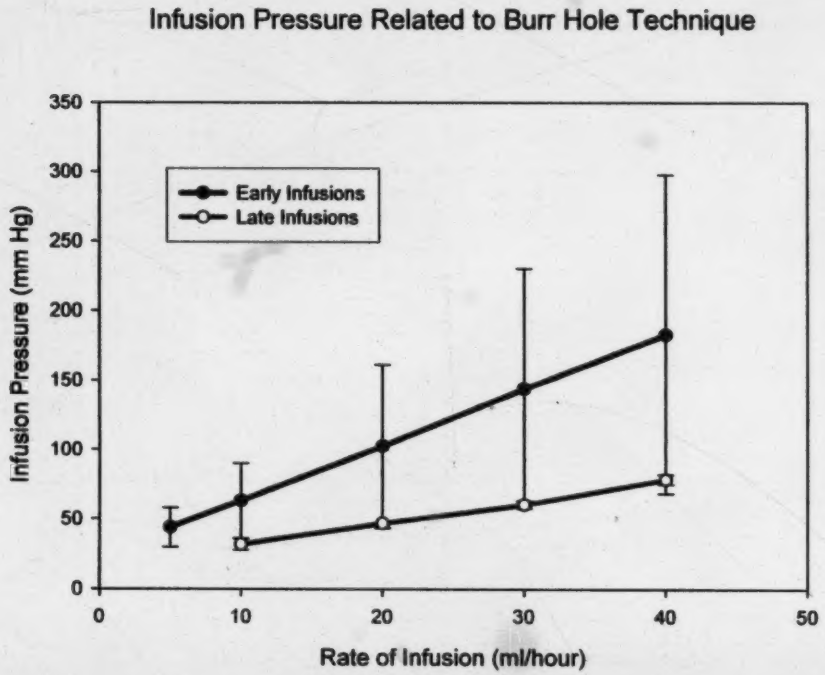

Figure 7-3. Comparison of the resistance to infusion by modifying the technique for accessing the calvarial diploë. The early burr holes were drilled using a hand twist drill, with or without curetting of the walls of the cancellous diploë. For late infusions, specific care was taken to prevent thrombus formation and open the vascular channels of the skull by infusing heparinized saline at a higher rate for the first 20 ml prior to conducting the lower rate infusion studies.

The resistance to infusion can be calculated by the infusion pressure divided by the rate of infusion. At 10 ml/hour, the resistance to infusion improved from 6.3 mm Hg/ml/hour to 3.2 mm Hg/ml/hour. At 20 ml/hour, the resistance decreased from 5.1 mm Hg/ml/hour to 2.4 mm Hg/ml/hour.

Cerebrospinal fluid is formed at a constant rate of approximately 20 ml/hour. To maintain the natural CSF volume, absorption must equal formation. The normal pressure driving CSF absorption is 5 to 10 mm Hg which is the difference between the intracranial pressure and the dural venous sinus pressure. Developing a system for the diversion of CSF into the calvarial diploë requires establishing a low resistance technique for intraosseous infusion. The lowest pressure required to infuse fluid at 10 ml/hour and 20 ml/hour in the porcine skull was 29 mm Hg and 40 mm Hg respectively – more than double the normal intracranial pressure. The resistance to calvarial infusion into the human skull at autopsy was studied in one patient. At 10 ml/hour, the resistance to human calvarial infusion was 1.4 mm Hg/ml/hour, less than half that found in the later porcine infusions. At 20 ml/hour, the resistance increased to 2.25 mm Hg/ml/hour (Figure 7-4). Thus, the driving pressure needed to infuse fluid at 10 ml/hour and 20 ml/hour was 14 mm Hg and 45 mm Hg respectively.

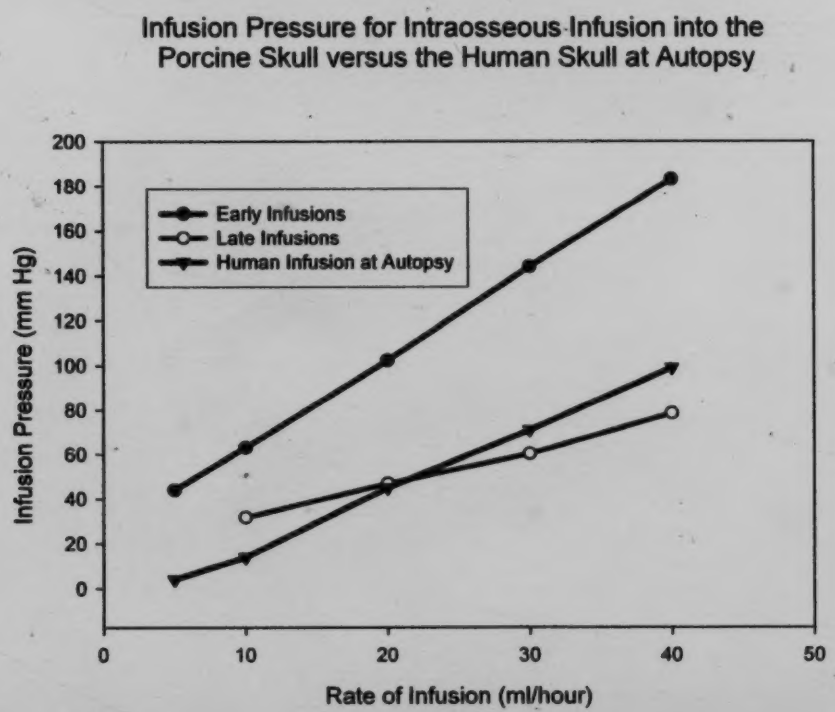

Figure 7-4. Human autopsy infusion as compared with early and late porcine infusions. At lower rates, the human skull offers less resistance to calvarial infusion, approaching the physiologic resistance to CSF absorption. Thrombus within the draining veins post-mortem likely increases the resistance at autopsy.

In clinical practice, the vascularity of the human skull is evident by the often robust bleeding from burr holes. The trabeculae of the cancellous diploë form open venous channels which communicate with diploic veins. In contrast, the porcine skull did not bleed as vigorously regardless of the techniques used for drilling burr holes into the diploic space. The trabeculae of the porcine skull are delicate: disruption of the trabeculae led to smearing and obstruction of the vascular channels, as demonstrated by histological studies. This may partially explain the increased resistance to infusion through the porcine skull as compared with the human skull. Additionally, Tocantins and O'Neill found that the intramedullary pressure corresponded closely with the pressure of the venous system draining the bone.[32] As thrombus occludes the venous system post-mortem, the increased resistance through the draining veins probably increases the driving pressure necessary to infuse fluid at any given rate of infusion. Presumably, the resistance to calvarial infusion would be lower in the living human skull and may approximate the normal resistance to CSF absorption. Future dynamic infusion studies into the human skull will answer this question.

The final four animals had a parenchymal intracranial pressure monitor inserted into either the ipsilateral or contralateral cerebral hemisphere prior to intraosseous infusion. This was done to establish the safety of calvarial infusions. Given the sometimes high infusion pressures necessary to deliver fluids at higher rates, we were concerned that increases in intraosseous pressure may led to increased venous pressure that could be transmitted to the brain parenchyma causing increased intracranial pressure. In these four animals, the rate of infusion was increased from 200 ml/hour up to 600 ml/hour with an infusion pressure as high as 740 mm Hg with no change in intracranial pressure.

CHAPTER EIGHT
AUTOPSY STUDIES

To determine the ability to transfer animal intraosseous infusion to human calvarial infusions, we conducted a series of studies into the human skull at the time of autopsy. This was valuable for the development of our intraosseous infusion device as well as to determine the anatomic pathway of and resistance to venous drainage from the human skull. Three autopsy studies were conducted. The first two focused on identifying the venous drainage of the skull, while the third was conducted to establish the pressure necessary to drive intraosseous infusion at set rates.

The first infusion study was carried out using the screw-type infusion device. A hand twist drill was used to drill a 6 mm deep burr hole through the outer table into the diploic space. The resistance changes as the drill passes through the outer table into the trabeculated diploë. We then used a hand tap to prepare the burr hole for the screw-type infusion device. Two silicone gaskets were used to enhance the seal of the infusion device with the skull since the screw-type infusion device was too tall for this shallow burr hole. Though great care was taken to preserve the integrity of the inner table, we felt the inner table crack as the infusion screw was tightened in place. Despite this complication, we continued with the hand infusion of India ink through the infusion device. The resistance to infusion was minimal and we were concerned we had infused ink into the epidural space. The calvarium was then removed to examine the under surface of the skull (Figure 8-1). The dura remains adherent to the inner surface of the skull when the calvarium is removed and needs to be reflected to visualize the epidural space. The epidural collection of ink is well appreciated. This patient had a particularly thin skull which contributed to this complication (Figure 8-2). Penetration through the inner table is the most important complication to prevent when developing an intraosseous infusion system into the calvarium since epidural extravasation of fluid could have fatal consequences.

Figure 8-1. Inner surface of the calvarium with the dura reflected. Two screw-type infusion devices are seen penetrating the inner table of the skull. The first infusion device was left in place following recognized violation of the inner table. The second device was used for the infusion of India ink. The ink is staining the epidural space.

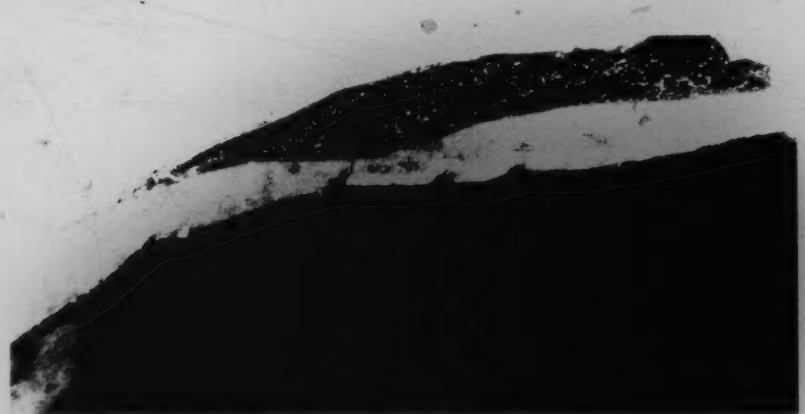

Figure 8-2. The calvarium of this patient was very thin, contributing to the complication of drilling through the skull into the epidural space.

As a result of this infusion study, we realized the limitation of the screw-type infusion device. The manifold style infusion device was then developed and used in subsequent autopsy infusions. A hand twist drill was again used to access the calvarial diploë. The manifold style infusion device was positioned over the burr hole and self tapping screws were used to secure the infusion device to the skull. A saw cut was made through the midline of the skull, opening the superior sagittal sinus, to allow external drainage of fluid and ink infused into the skull.

Water initially was hand flushed through the infusion device. To better visualize the effluent fluid from the sagittal sinus, India ink was infused through the infusion device. Ink flowed rapidly from the opening in the sagittal sinus more posteriorly thereby documenting the connection between the diploic space and the superior sagittal sinus (Figure 8-3 and Figure 8-4). We then removed the calvarium and examined the dural veins as well as the epidural and subdural space. The dural veins in close proximity to the infusion site were back filled with ink, as was the superior sagittal sinus. There was no extravasation of ink into the epidural or subdural space.

Figure 8-3. The manifold style infusion device is secured to the right parietal bone 2 cm behind the coronal suture. India ink infused into the calvarial diploë is seen to drain from the saw-cut through the sagittal sinus.

Figure 8-4. Close-up picture of the saw-cut through the occipital bone and sagittal sinus. India ink is seen draining easily from the sagittal sinus.

The third autopsy infusion was performed to determine the resistance to infusion through the human calvarium. The manifold style infusion device was secured to the skull after drilling a 6 mm deep burr hole into the calvarial diploë. Water was infused using a syringe pump at set rates of infusion from 5 ml/hour up to 40 ml/hour. An automated transducer measured the pressure required to deliver fluids at these set rates. We found that fluid could be infused into the calvarial diploë at up to 14 ml/hour with an infusion pressure of 20 mm Hg (Figure 8-5).

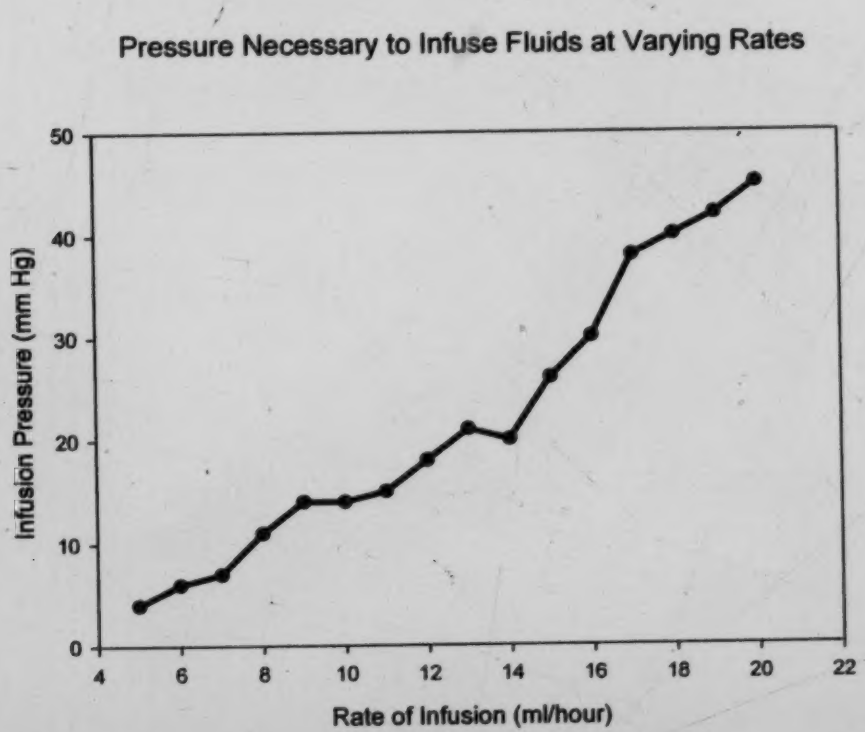

Figure 8-5. The infusion pressure required to infuse water at pre-determined rates of infusion increases linearly with infusion rate. The normal driving force for CSF absorption is between 10 and 20 mm Hg.

The relationship between rate of infusion and infusion pressure at autopsy demonstrates the potential for this technique to divert CSF at physiologic rates for intraosseous absorption. It is likely that the resistance to infusion in the living human

skull is even lower than that found at the time of autopsy. Further infusion studies into the human skull will help answer this question and better demonstrate the potential for intraosseous diversion of CSF as an indirect access to the absorptive sites along the superior sagittal sinus.

CHAPTER NINE
CONCLUSIONS

Before we begin to consider the calvarial diploë as a potential site for the intraosseous diversion and absorption of cerebrospinal fluid, we must first evaluate the capacity of the skull to absorb fluids into the central circulation. It was previously believed that a functioning medullary cavity was necessary for intraosseous infusions.[13, 14, 16, 19, 31, 72] Successful infusions into the calcaneus revealed that a medullary cavity is not required.[36-38] Dextrose infusions clearly indicate the absorptive capacity of the calvarial diploë. The skull is richly vascular with venous drainage via emissary and diploic veins into dural channels and venous sinuses.[4, 34] The pigs' insulin response to maintain serum glucose limited the usefulness of dextrose infusions. Large volume infusions were necessary and given the high resistance, infusions took 16-86 seconds (14-75 ml/min or 840-4500 ml/hour). This is in concordance with intraosseous infusion rates in the literature which range from 0.4-80 ml/min (24-4800 ml/hour) by gravity, and up to 150 ml/min (9000 ml/hour) by syringe injection.

In order to demonstrate the rapid delivery of infused fluids into the central circulation, a low volume non-biologic marker was valuable. Technetium 99^{m} is routinely used clinically as a radioactive tracer that is distributed throughout the body. Technetium infusions successfully demonstrated the rapid uptake of infusate into the central circulation, though due to leakage from the screw-type infusion device the delivery of technetium was variable. This variable delivery led to inconsistent results. Results were considerably better using the manifold style infusion; however, handling restrictions using a radioactive tracer limited the usefulness of technetium.

FITC-Dextran infusions validated the dextrose and technetium infusion results. Low volume injections demonstrated rapid central delivery matching the delivery through a peripheral ear vein. FITC-Dextrans are stable, water-soluble, and non-toxic which makes them extremely valuable as a physiologic tracer. Using large (D70) molecular weight dextrans which remain within the vascular space, we had a reliable marker of

systemic uptake. The additional benefit is the ability of fluorescein to reveal any leakage from the infusion site or elsewhere from the skull. The manifold style infusion device was used for all FITC-Dextran infusions. This device provided a better seal at the interface with the skull, was easier to secure, and is suitable for human infusions.

In addition developing an effective infusion device, we investigated a number of techniques to best access the diploic space of the porcine skull. Infusion pressure studies revealed that slow hand twist drill burr holes least disrupted the native architecture of the trabeculated diploë. This led to the lowest resistance to infusion. The driving pressure to infuse fluids at 10 ml/hour was 29 mm Hg. In contrast, we were able to infuse fluids up to 14 ml/hour into the human skull with a driving pressure of 20 mm Hg. This suggests that the human skull may have a greater capacity to absorb fluids than the porcine skull.

Cerebrospinal fluid is formed at up to 20 ml/hour. The best CSF shunt system would allow drainage to match formation. It is our aim to create an intra-calvarial infusion system (ICIS) to permit diversion of CSF without the need for long distal catheters or complex valves. Future dynamic human infusions may demonstrate that the infusion pressure necessary to drive intra-calvarial infusions is similar to the natural driving force for CSF absorption across the arachnoid granulations. Such findings would lead to novel treatment options in the management of hydrocephalus.

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